The evidence relating short-term $PM_{10-2.5}$ exposure and cardiovascular outcomes has expanded since the last review and now includes additional epidemiologic studies reporting positive associations with IHD, HA, and arrhythmia. However, key uncertainties related to copollutant confounding and exposure measurement error remain. In addition, uncertainties remain with respect to the biological plausibility of ED visits and hospital admissions for IHD and arrhythmia. Thus, when considered as a whole, the epidemiologic, CHE and animal toxicological evidence continues to be suggestive but not sufficient to infer a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects. The evidence supporting this determination of causality is discussed below and summarized in Table 6-62, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

Studies published since the 2009 PM ISA provide additional evidence of an association between short-term exposure to $PM_{10-2.5}$ and ED visits and/or hospital admissions for IHD. In the MCAPS study, $PM_{10-2.5}$ concentrations were associated with an increase in hospital admissions for IHD on the same day (Powell et al., 2015) and the association was unchanged in copollutant models adjusting for $PM_{2.5}$. Qiu et al. (2013) also observed a positive association, which persisted but lost precision after adjustment for $PM_{2.5}$. In Kaohsiung, Taiwan, Chen et al. (2015b) considered nearly 23,000 hospital admissions for IHD and reported positive associations on cool and warm days. The observed associations were generally robust to adjustment for NO_2, SO_2, CO, and O_3 in copollutant models. Thus, there are a few studies using copollutant models that suggest an independent effect of $PM_{10-2.5}$ on IHD-related HA. However, uncertainties with respect to copollutant confounding remain due to the overall evidence base for an independent effect of $PM_{10-2.5}$ being quite limited.

There are also a limited number of studies providing evidence of an associations between short-term exposure to $PM_{10-2.5}$ and ED visits and hospital admissions for arrhythmia (Section 6.3.4). However, appreciable uncertainties in these results remain given that none of these studies examined the potential for copollutant confounding with other size fractions of PM, and gaseous copollutant results are from a small number of studies conducted in Asia. It is also important to note that the approaches used to estimate $PM_{10-2.5}$ concentrations vary across the epidemiologic studies mentioned above (both for arrhythmia and IHD). Methods include using the difference of county-level averages of PM_{10} and $PM_{2.5}$ and the difference of PM_{10} and $PM_{2.5}$ measured at co-located monitors. It remains unclear how exposure measurement error might be impacted by each of these approaches.

A small number of CHE, epidemiologic panel, and animal toxicological studies provides some biological plausibility for a sequence of events that could potentially lead to $PM_{10-2.5}$-related ED visit and hospital admissions (Section 6.3.1). However, the evidence supporting most of the individual events in these pathways is quite limited and some of the epidemiologic panel studies used to support these pathways have the same measurement error uncertainties mentioned above. Also, when the evidence is evaluated as a whole, with the exception of small reproducible changes in BP (Section 6.3.6), the results of experimental and epidemiologic panel studies are largely inconsistent, or only provided limited

evidence of a relationship between cardiovascular endpoints and short-term $PM_{10-2.5}$ exposure. Thus, while there is more evidence for biological plausibility than in the 2009 PM ISA, this body of evidence is still quite limited and important uncertainties remain.

In summary, there were a small number of epidemiologic studies reporting positive associations between short-term exposure to $PM_{10-2.5}$ and cardiovascular-related ED visits and HA. However, there was limited evidence to suggest that these associations were biologically plausible, or independent of copollutant confounding. It also remains unclear how the approaches used to estimate $PM_{10-2.5}$ concentrations in epidemiologic studies may impact exposure measurement error. Taken together, the **evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposures and cardiovascular effects.**

Table 6-62 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Evidence from multiple epidemiologic studies is generally supportive but not entirely consistent	Increases in ED visits and hospital admissions for IHD in multicity studies Increases in cardiovascular mortality in multicity studies conducted in the U.S., Europe, and Asia.	Powell et al. (2015); Section 6.3.2 Section 6.3.8	12.8 µg/m^3
Generally, consistent evidence from CHE studies	Small consistent changes in blood pressure	Section 6.3.6.2	~75.2-200 µg/m^3
Limited and supportive evidence from panel, controlled human exposure, and toxicological studies	Limited evidence for changes in HRV, systemic inflammation, coagulation factors, vascular function	Section 6.3.9 Section 6.3.10 Section 6.3.11 Section 6.3.12	See Tables in identified sections

Table 6-62 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{10-2.5}$ association	$PM_{10-2.5}$ associations are generally robust, but there are some instances of attenuation in copollutant models with gaseous pollutants and $PM_{2.5}$. However, there is limited information on the correlation between $PM_{10-2.5}$ and gaseous pollutants complicating the interpretation of results. Copollutant analyses with cardiovascular mortality are limited to studies conducted in Europe and Asia and indicate that $PM_{10-2.5}$ associations generally remain positive, although attenuated in some instances. When reported, correlations with gaseous copollutants were primarily in the low (r < 0.4) to moderate ($r \geq 0.4$ or < 0.7) range.	Powell et al. (2015); Qiu et al. (2013); Chen et al. (2015b) Figure 6-31	
Uncertainty regarding exposure measurement error	Across studies $PM_{10-2.5}$ concentrations are measured using a number of approaches (i.e., directly measured from dichotomous sampler, different between PM_{10} and $PM_{2.5}$ at collocated monitors, and difference of area-wide concentrations of PM_{10} and $PM_{2.5}$), which have not been compared in terms of whether they have similar spatial and temporal correlations.		
Limited evidence for biological plausibility of cardiovascular effects	Studies for a given health endpoint are largely inconsistent, or only provide limited evidence of a relationship between cardiovascular endpoints and $PM_{10-2.5}$ exposure. Some epidemiologic panel studies are also subject to the exposure measurement error discussed in this section.	Section 6.3.1 Figure 6-30	

a = Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

b = Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

c = Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.4 Long-Term $PM_{10-2.5}$ Exposure and Cardiovascular Effects

The evidence relating to the long-term effects of exposure to $PM_{10-2.5}$ on the cardiovascular system was characterized as "inadequate to infer the presence or absence of a causal relationship" in the 2009 PM ISA (U.S. EPA, 2009). A cause specific mortality study found a positive association with CHD

mortality among women enrolled in AHSMOG while another study of women (WHI) reported no association between $PM_{10-2.5}$ and cardiovascular events. Experimental studies demonstrating a direct effect of $PM_{10-2.5}$ on the cardiovascular system were lacking.

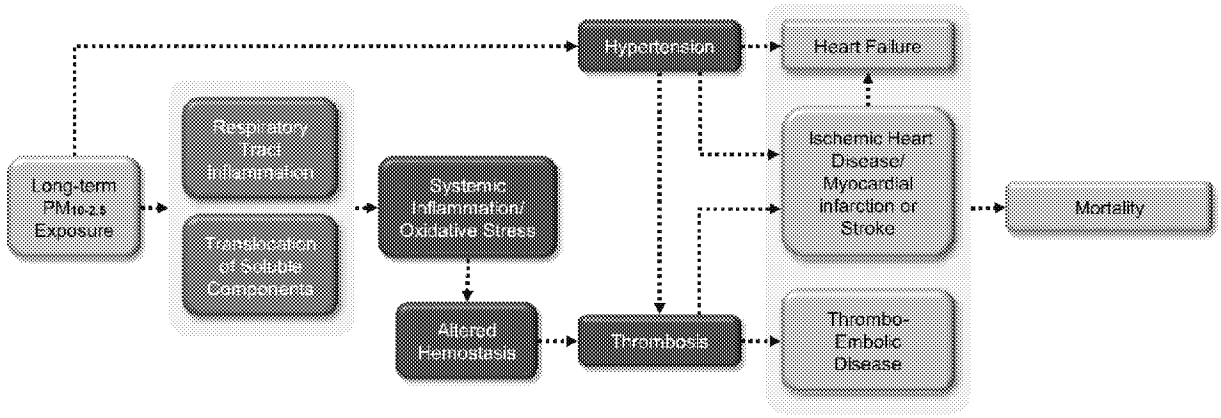
Evidence published since the completion of the 2009 PM ISA is also suggestive of a causal relationship between long-term exposures to $PM_{10-2.5}$ and cardiovascular effects. Since the publication of the 2009 PM ISA, the epidemiologic literature has grown and evidence is currently available on the relationship between exposure to long-term $PM_{10-2.5}$ and cardiovascular outcomes including MI and stroke, blood pressure and atherosclerosis. However, the overall epidemiologic evidence base is limited and uncertainties remain with respect to the potential for co-pollutant confounding. In addition, there continues to be a lack of toxicological evidence to support the associations reported in epidemiologic studies.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-tern $PM_{10-2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-tern $PM_{10-2.5}$ exposure (Section 6.4.1). Following this discussion, the health evidence relating long-tern $PM_{10-2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.4.2), heart failure and impaired heart function (Section 6.4.3), cerebral vascular disease and stroke (Section 6.4.4) atherosclerosis (Section 6.4.5), blood pressure and hypertension (Section 6.4.6), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.4.7) and cardiovascular-related mortality (Section 6.4.8). The evidence for an effect of $PM_{10-2.5}$ exposure on systemic inflammation and oxidative stress is also discussed (Section 6.4.9). Finally, the collective body of evidence is integrated across and within scientific disciplines[65], and the rationale for the causality determination is outlined in Section 6.4.10.

6.4.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from long-term inhalation exposure to $PM_{10-2.5}$. Figure 6-33 graphically depicts these proposed pathways as a continuum of pathophysiological responses- connected by arrows- that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{10-2.5}$ may lead to these cardiovascular events also provides some biological plausibility for the epidemiologic results reported later in Section 6.4. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.4.

[65] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 6-33 Potential biological pathways for cardiovascular effects following long-term exposure to $PM_{10-2.5}$.

When considering the available health evidence, there is a plausible pathway connecting long-term exposure to $PM_{10-2.5}$ to the apical events reported in epidemiologic studies (Figure 6-33). This pathway is described below and generally begins as respiratory tract inflammation leading to systemic inflammation.[66]

Long-term inhalation exposure to $PM_{10-2.5}$ may result in respiratory tract inflammation and oxidative stress (CHAPTER 5). Inflammatory mediators such as cytokines produced in the respiratory tract can potentially enter the circulatory system where they may cause distal pathophysiological responses such as changes in hemostasis (see Section 6.1.1). Thus, it noteworthy that following long-term exposure to $PM_{10-2.5}$, there is limited evidence from an epidemiologic study for systemic inflammation (Lanki et al., 2015) and altered hemostasis (Lanki et al., 2015). Therefore, thrombosis could conceivably occur, potentially contributing to the development of IHD, stroke, or thromboembolic disease elsewhere in the body (as previously described in Section 6.1.1). There is also evidence from epidemiologic studies that long-term exposure to $PM_{10-2.5}$ is associated with elevated blood pressure/hypertension risk (Chen et al., 2015a; Mu et al., 2014). Hypertension may also result in pathways that can contribute to the development of IHD, HF, stroke, or thromboembolic disease elsewhere in the body (as previously described in Section 6.1.1).

[66] It is also possible that soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

Taken together, there is a small amount of evidence connecting long-term $PM_{10-2.5}$ exposure to cardiovascular health effects. That said, gaps in the proposed pathway exist. For example, there is a lack of evidence for how long-term $PM_{10-2.5}$ exposure may result in hypertension. Thus, there is only limited biological plausibility for the apical results reported in epidemiologic studies following long-term $PM_{10-2.5}$ exposure. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.4.10).

6.4.2 Ischemic Heart Disease and Myocardial Infarction

Ischemic heart disease (IHD) is typically caused by atherosclerosis, which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle potentially leading myocardial infarction (MI) or heart attack (Section 6.2.2). The evidence relating to the effect of $PM_{10-2.5}$ on the cardiovascular system included in the 2009 PM ISA was limited to a study of post-menopausal women enrolled in the WHI. The primary objective of this study (Miller et al., 2007) was to examine the cardiovascular health effects of long-term exposure to $PM_{2.5}$; however, results for $PM_{10-2.5}$ were also reported. No association between $PM_{10-2.5}$ and cardiovascular events was observed [HR: 0.99 (95%CI: 0.95, 1.03)]. Since the completion of the 2009 PM ISA, several epidemiologic studies reporting associations with $PM_{10-2.5}$, including some with comparable female populations, have been published. Among the limited number of studies currently available, positive associations were not consistently observed (Table 6-63, Figure 6-34).

Table 6-63 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
(Miller et al., 2007) 36 metro areas, U.S. Prospective cohort $PM_{10-2.5}$: 2000 Follow-up: 1994-1998	WHI N = 65,893, women Median follow-up: 6 yrs	Annual avg of closest monitor (2000) Most participants within 10 km of monitor	NR	CVD event (MI, coronary revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Multipollutant model: $PM_{2.5}$, CO, SO2, NO_2, O_3 Copollutant correlations: NR
†(Hart et al., 2015b) U.S. (all contiguous states) Prospective cohort $PM_{10-2.5}$: 1989-2006 (sensitivity analyses restricting data to the years 2000-2006) Follow-up: 1988-2006	NHS N = 114,537 Follow-up: ~16 yrs	Annual avg, spatiotemporal model, $PM_{10-2.5}$ estimated by subtraction of monthly $PM_{2.5}$ from PM_{10}; time-varying exposure assigned based on residential address (C-V R^2 = 0.59, PM_{10}; 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post 1999, respectively)	Mean 1989-2006: 8.7 (SD 4.5) Mean 2000-2006: 7.3 (SD 4.1)	Self-reported physician diagnosed CHD	Copollutant correlations: $PM_{2.5}$: r = 0.2; PM_{10}: r = 0.86
†(Puett et al., 2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988-2002 Follow-up: 1989-Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg estimated using spatiotemporal models for 2 time periods; C-V R^2 = 0.39, precision = 5.5 µg/m³) see Yanosky et al. (2009) for details	Mean: 10.1 (SD: 3.3) IQR: 4.3	Non-fatal MI (medical record review)	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR

Table 6-63 (Continued): Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Cesaroni et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008-2011 Follow-up: 1992-2007, depending on cohort	ESCAPE N = 100,166 Avg follow-up: 11.5 yrs	Annual avg, LUR with measurements from 20 locations per study area Model performance R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	IHD (hospital records) ICD9 410, 411	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR
(Hoffmann et al., 2015) Prospective cohort $PM_{10-2.5}$: 2008-2009 Outcome: 2000/03-2012	HNR study N = 4,433	Multi-year avg (baseline) using LUR to estimate concentration at residential address	9.99 (SD: 1.83)	Self-reported coronary events with expert evaluation	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR
†(Tonne et al., 2015) Greater, London Prospective cohort $PM_{10-2.5}$: 2003-2010 Follow-up: 2003/07 - 2010	MINAP (MI Survivors) N = 18,138 Avg follow-up 4 yrs	Annual avg estimated using dispersion models (20 by 20 m grid) time-varying exposure assigned within 100 m of patients' residential postal code centroid	Mean: 8.6 (SD: (0.7); IQR: 0.9	Readmission for STEMI or non-STEMI and death combined	Copollutant model: NR Copollutant correlations: $PM_{2.5}$ r = 0.70; PM_{10} r = 0.87; O_3 r = -0.88, NO_X r = 0.94; NO_2 r = 0.93

Avg = average, C-V = cross validation, ESCAPE = European Study of Air Pollution Exposure, HPFU = Health Professionals Follow-up Study, HNR = Heinz Nixdorf Recall study, LUR = land use regression, MI = myocardial infarction, NHS = Nurses' Health Study, N, n = number of subjects, NR = not reported, SD = standard deviation, STEMI = ST elevation myocardial infarction

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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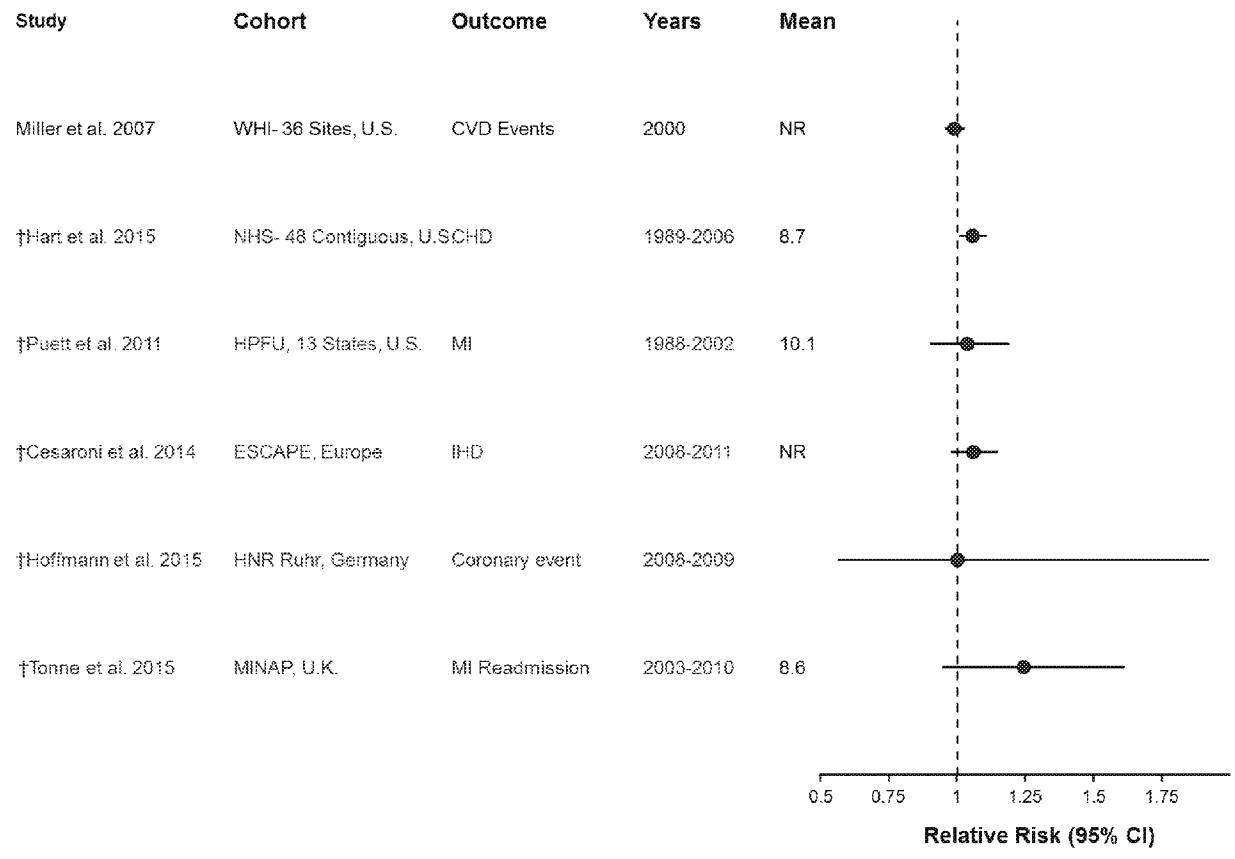
Hart et al. (2015b) examined data from the NHS, a cohort of women, 30-55 years old at enrollment, and observed positive associations of $PM_{10-2.5}$ with CHD [HR: 1.06 (95% CI: 1.01, 1.11)] Associations were less precise and somewhat attenuated in a sensitivity analysis restricted to exposure data that were relatively complete. Associations between $PM_{10-2.5}$ and CHD [HR: 1.07 (95%CI: 1.00, 1.14) vs. 0.96 (95%CI: 0.92, 1.0)] were present among women with diabetes, respectively. Effect modification by diabetes did not persist for CHD when analyses were restricted to the years with relatively complete exposure data. Larger associations of $PM_{10-2.5}$ with CHD were observed in the northeast compared to other regions. In a study of male health professionals Puett et al. (2011), a small increased risk for nonfatal MI was observed [HR: 1.04 (95%CI: 0.90, 1.19)]. There was no association after adjustment for $PM_{2.5}$, however [HR: 1.00 (95%CI: 0.85, 1.18)].

Cesaroni et al. (2014) reported an increased risk for the association between $PM_{10-2.5}$ and IHD [HR: 1.06 (0.98, 1.15)] in their meta-analysis of the 11 cohorts in the ESCAPE project. Heterogeneity in the effect estimates was observed across cohorts. In a separate analysis of one of the ESCAPE cohorts, Hoffmann et al. (2015) reported an inverse association of $PM_{10-2.5}$ exposure with coronary events [HR: 0.78 (95%CI: 0.33, 1.82)] in fully adjusted models that considered covariates including noise. Tonne et al. (2015) reported an association between $PM_{10-2.5}$ and readmission for MI in the MINAP study in the U.K. [HR: 1.24 (95%CI: 0.95, 1.61)].



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-16 (U.S. EPA, 2018). CTS = California Teachers Study; ESCAPE = European Study of Cohorts for Air Pollution; HPFU = Health Professionals Follow-up Study; IHD = Ischemic Heart Disease; HNR = Heinz Nixdorf Recall study; MINAP = Myocardial Ischemia National Audit Project; MI = Myocardial Infarction; NR=not reported; NHS = Nurses' Health Study; WHI = Women's Health Initiative.

Figure 6-34 Associations between long-term exposure to $PM_{10-2.5}$ and ischemic heart disease. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

6.4.3 Heart Failure and Impaired Heart Function

There were no studies of the effect of long-term exposure to $PM_{10-2.5}$ on heart failure or impaired heart function in the 2009 PM ISA (U.S. EPA, 2009).

6.4.3.1 Epidemiologic Studies

The E/E ratio is the ratio of peak early diastolic filling velocity to peak early diastolic mitral annulus velocity and a value less than eight indicates normal diastolic function and left atrial volume index (LAVI) is an indicator of diastolic function severity (Section 6.3.5). D'Souza et al. (2017) reported small imprecise increases in RV mass overall [0.91 g (95%CI: -2.95, 5.00] but larger increases were found among current smokers [2.05 g (95%CI: 0.23, 3.86] and those with emphysema [3.18 g [95%CI: 0.91, 5.68]. Ohlwein et al. (2016) conducted a cross-sectional analysis of the SALIA cohort to determine the association of long-term $PM_{10-2.5}$ with these two metrics. The mean ratios comparing 3rd to the 1st quartile of exposure for $PM_{10-2.5}$ were 1.03 (95%CI: 0.89, 1.18) for E/E and 1.06 (95%CI: 0.92, 1.21) for LAVI.

Table 6-64 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†(Ohlwein et al., 2016) Cross-sectional $PM_{10-2.5}$: 2008-2009 Baseline: 2007/10	SALIA N = 402 69-79 yrs	LUR fit from differences between PM_{10} and $PM_{2.5}$ concentrations to estimate exposure at residence Model fit R2 = 0.66, cross-validation R2 = 0.57	Median: 9.1 (IQR: 8.6-10.4)	E/E" ratio LAVI (Tissue Doppler)	Correlations: NR
†(D'Souza et al., 2017) $PM_{10-2.5}$ mass and components	MESA N = 1,490 45-84 yrs	LUR fit from differences between P_{M10} and $PM_{2.5}$ concentrations to estimate 5-yr concentration at residence	Mean: 4.9 SD: 1.6	RV mass, volume, EF	2-pollutant models $PM_{2.5}$ and NO_2

MESA = Multi Ethnic Study of Atherosclerosis; SALIA = Study on the Influence of Air Pollution on Lung ; LUR = land use regression; E/E' = ratio of peak early diastolic filling velocity and peak early diastolic mitral annulus velocity; LAVI = Left Atrial Volume Index; RV = right ventricle; EF = ejection fraction

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.4.3.2 Toxicology Studies of Impaired Heart Function

In the 2009 PM ISA there was one study (Lemos et al., 2006) that reported heart muscle hypertrophy for Balb/c mice exposed to PM_{10} for 4 months. Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that short-term $PM_{10-2.5}$ exposure in rats resulted in thickening of the coronary artery wall ($p < 0.05$). However, the authors did not report increases in expression of two genes typically associated with cardiac damage: Acta1 and Col3a. Nonetheless, there is limited evidence from animal toxicological studies for the potential for decreases in heart function following long-term $PM_{10-2.5}$ exposure. More information on this recently published study can be found in Table 6-65 below.

Table 6-65 Study specific details from toxicological studies of long-term $PM_{10-2.5}$ exposure and impaired heart function impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Sprague-Dawley rats, M n = 4 per group)	Inhalation of 32 µg/m^3 $PM_{10-2.5}$ collected from a high traffic and industrial area north of Mexico City in early summer and exposed for 5 h/day, 4 days/week for 8 weeks	Coronary wall thickness Acta1 and Col3a gene expression

n = number, h = hour, d = day, week = week, M = male, f = female, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.4.4 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries (Section 6.3.35). Only the WHI analysis reporting a positive association with stroke was available for inclusion in the 2009 PM ISA. Of the limited number of recent epidemiologic studies examining the relationship between $PM_{10-2.5}$ and stroke, there were some observations of positive associations (Table 6-66, Figure 6-35).

Table 6-66 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and stroke.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{10-2.5}$: 2000 Follow-up: 1994-1998	WHI observational cohort N = 65,893 Median follow-up: 6 yrs	Annual avg of closest monitor (2000) Most women within 10 km of monitor	NR	CVD event (MI, coronary revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†(Hart et al., 2015b) U.S. (all contiguous states) Prospective cohort $PM_{10-2.5}$: 1989-2006 (sensitivity analyses restricting data to the years 2000-2006) Follow-up: 1988-2006	NHS N = 114,537 Follow-up: ~16 yrs	Annual avg, spatio-temporal model, $PM_{10-2.5}$ estimated by subtraction of monthly $PM_{2.5}$ from PM_{10}; time-varying exposure assigned based on residential address (C-V R^2 = 0.59, PM_{10} ; 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post 1999, respectively)	Mean 1989-2006: 8.7 (SD 4.5) Mean 2000-2006: 7.3 (SD 4.1)	Self-reported physician diagnosed stroke	Copollutant model: NR Copollutant correlations: $PM_{2.5}$: r = 0.2; PM_{10}: r = 0.86
†(Puett et al., 2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988-2002 Follow-up: 1989-Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg estimated using spatio-temporal models for 2 time periods; C-V R^2 = 0.39, precision = 5.5 µg/m³) see Yanosky et al. (2009) for details	Mean: 10.1 (SD: 3.3) IQR: 4.3	IS, HS ((medical record review)	Copollutant model: $PM_{2.5}$ Copollutant correlations: NR

Table 6-66 (Continued): Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and stroke.

Study	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutants Examined
†(Stafoggia et al., 2014) 11 Cohorts Europe $PM_{10-2.5}$: 2008-2011 Outcome: 1992/2007–2010	ESCAPE N = 105,025	Annual exposure at residence using LUR fit to $PM_{10-2.5}$ estimated from the difference between PM_{10} and $PM_{2.5}$ model fit R^2 avg 0.68 (0.32-0.81), see (Eeftens et al., 2012)	6-17	Stroke incidence using hospital discharge data	Copollutant model: NR Copollutant correlations: NR
†(Hoffmann et al., 2015) Prospective cohort $PM_{10-2.5}$: 2008-2009 Outcome: 2000/03-2012	HNR study N = 4,433	Multi-year avg (baseline) using LUR fit to $PM_{10-2.5}$ estimated from the difference between PM_{10} and $PM_{2.5}$, residential address	9.99 (SD: 1.83)	Self-reported stroke with expert evaluation	Copollutant model: NR Copollutant correlations: NR

Avg = average, BRFSS = Behavioral Risk Factor Surveillance System, C-V = cross validation, ESCAPE = European Study of Air Pollution Exposure, HS = hemorrhagic Stroke, IS = Ischemic Stroke, HPFU = Health Professionals Follow-up Study, LUR = land use regression, NHS = Nurses' Health Study, N, n = number of subjects, NR = not reported, HNR = Heinz Nixdorf Recall study, SD = standard deviation

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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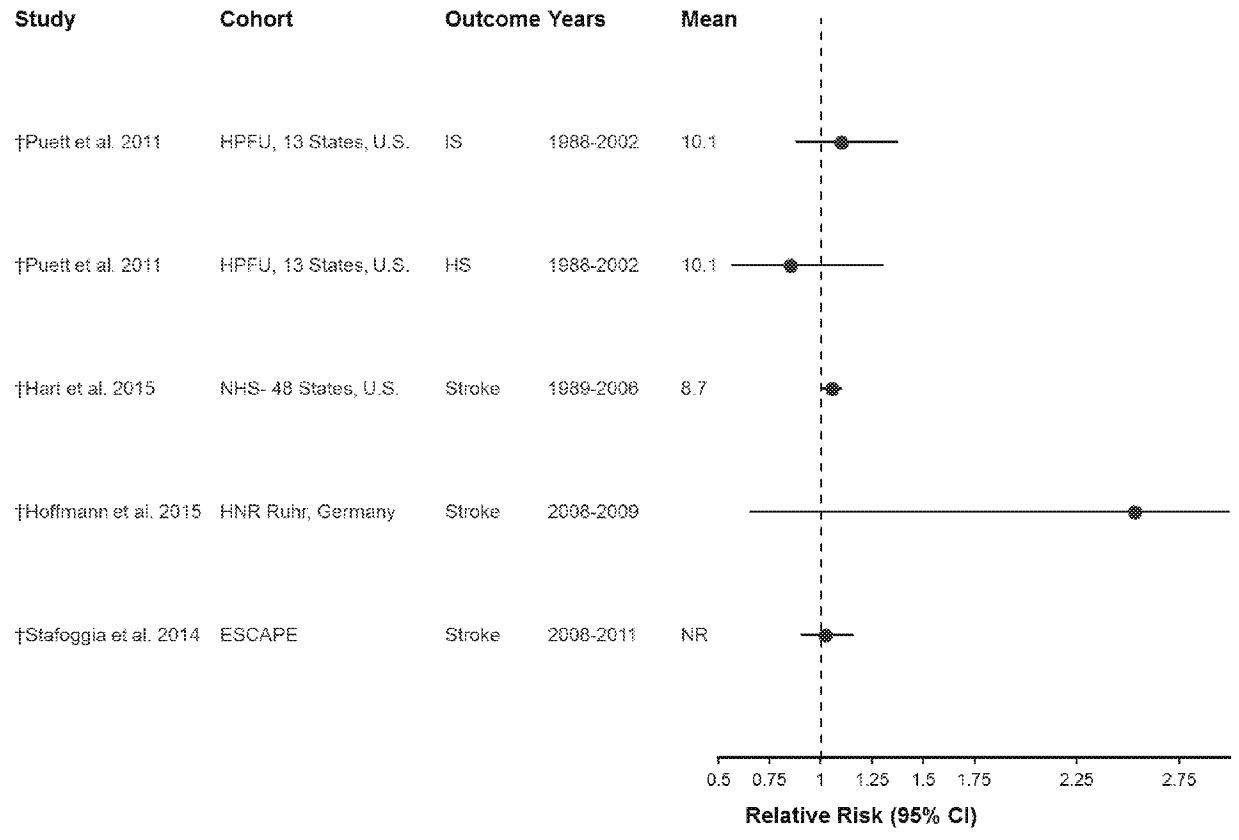
Hart et al. (2015b) examined data from women enrolled in the NHS and observed positive associations of $PM_{10-2.5}$ stroke [HR: 1.05 (95%CI: 1.00, 1.10)]. Larger associations between $PM_{10-2.5}$ and stroke [HR: 1.09 (95%CI: 1.00, 1.17)] were present among women with diabetes. Effect modification by diabetes persisted for stroke when analyses were restricted to the years with relatively complete exposure data. Larger associations of $PM_{10-2.5}$ with stroke were observed in the northeast compared to other regions, but not in the south. These strong associations in the northeast were even stronger in sensitivity analyses restricted to years with complete exposure data. Among male health professionals, Puett et al. (2011) reported an imprecise (n = 230 cases) increased risk for ischemic stroke [HR: 1.10 (95%CI: 0.88, 1.37and no association with hemorrhagic stroke [HR: 0.85 (95%CI: 0.56, 1.31)] in their basic model. A fully adjusted model that included comorbidities such as hypertension and diabetes returned similar results. The association between $PM_{10-2.5}$ and ischemic stroke strengthened after adjustment for $PM_{2.5}$ [HR: 1.31 (95%CI: 0.99, 1.72)]. Confidence intervals were wide due to small case numbers (N = 230 ischemic strokes), however.

No association of $PM_{10-2.5}$ was observed on incident stroke in the 11-cohort European Escape study [HR: 1.02 (95%CI: 0.90, 1.16)] (Stafoggia et al., 2014), although a separate analysis of one of the included cohorts (HNR) indicated a potential relationship between $PM_{10-2.5}$ and incident stroke. Although confidence intervals were wide Hoffmann et al. (2015), reported a strong positive association in this study [HR: 2.53 (95%CI: 0.65, 9.84)].

As shown in Figure 6-35, associations between $PM_{10-2.5}$ were not consistently observed in epidemiological of coronary events, CHD or stroke. Overall, the number of studies is limited and model performance is generally lower than the model performance for $PM_{2.5}$.



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5- $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-25 (U.S. EPA, 2018). HS = hemorrhagic Stroke, IS = Ischemic Stroke, HPFU = Health Professionals Follow-up Study, NHS = Nurses' Health Study, NHR = Heinz Nixdorf Recall, ESCAPE = European Study of Air Pollution Exposure.

Figure 6-35 Associations between long-term exposure to $PM_{10-2.5}$ and stroke. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

6.4.5 Atherosclerosis

Atherosclerosis is the process of plaque buildup into lesions on the walls of the coronary arteries that can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. The development of atherosclerosis is dependent on the interplay between plasma lipoproteins, inflammation, endothelial activation, and polymorphonucelar leukocyte attraction to the endothelium, extravasation, and lipid uptake. Additional information on atherosclerosis can be found in Section 6.2.4.

Increased cIMT is an indicator of atherosclerosis. An inverse cross-sectional association between long-term exposure to $PM_{10-2.5}$ and cIMT was observed in the ESCAPE study [-0.28% difference (95%CI: -1.16, 0.61)] (Perez et al., 2015) (Table 6-67).

Table 6-67 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutants Examined
(Perez et al., 2015) Cross-sectional 4 European Cohorts: IMPROVE, HNR, KORA, REGICOR $PM_{10-2.5}$: 2008-2009 Outcome: 1997-2009	ESCAPE N = 9,183	Annual avg estimated using LUR (20 monitors) at residence Model fit R^2 = 0.71 (median, cross validation R^2 results 8-11% lower, see (Eeftens et al., 2012)	IMPROVE: Mean 7.1 (SD: 3.0), IQR: 3.0 HNR: Mean 10.0 (SD: 1.8), IQR: 1.9 KORA: Mean 6.2 (SD: 1.1), IQR: 1.2 REGICOR: Mean 15.6 (SD: 2.7), IQR: 3.7	cIMT	IMPROVE: $PM_{2.5}$ r = 0.62; $PM_{2.5}$abs r = 0.63; NO_2 r = 0.6; NO_X r = 0.55 HNR $PM_{2.5}$ r = 0.68; $PM_{2.5}$abs r = 0.72; NO_2 r = 0.46; NO_X r = 0.42 KORA: $PM_{2.5}$ r = 0.28; $PM_{2.5}$abs r = 0.83; NO_2 r = 0.79; NO_X r = 0.85 REGICOR: $PM_{2.5}$ r = 0.12; $PM_{2.5}$abs r = 0.11; NO_2 r = 0.09; NO_X r = 0.15

cIMT = carotid intima media thickness, ESCAPE = European Study of Cohorts for Air Pollution, HNR = Heinz Nixdorf Recall, IQR = interquartile range, KORA =, REGICOR =, LUR = land use regression

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.4.6 Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm hg or a diastolic blood pressure above 90 mm hg with the clinically relevant consequence of chronically high blood pressure defined as hypertension (Section 6.2.7). There were no studies of the effect of $PM_{10-2.5}$ on blood pressure, hypertension or related effects on the renal system reviewed in the 2009 PM ISA.

6.4.6.1 Epidemiologic Studies

A limited number studies examined the relationship between $PM_{10-2.5}$ and blood pressure or hypertension among adults. Fuks et al. (2014) reported null associations with use of blood pressure lowering medication [OR: 0.99 (95%CI: 0.93, 1.05)] and hypertension [OR: 1.00 (95%CI: 0.94, 1.06)] in the ESCAPE cohort. Both small (relative to the size of the confidence interval) decreases and small increases in SBP and DBP were also observed in ESCAPE providing little support for an effect on blood pressure. A study conducted in Taiwan where mean $PM_{10-2.5}$ concentration was 21.2 $\mu g/m^3$ showed no effect on SBP but reported elevated DBP and an increased risk of hypertension in association with $PM_{10-2.5}$ (Chen et al., 2015a).

6.4.6.2 Toxicology Studies of Changes in Blood Pressure (BP)

There were no studies in the 2009 PM ISA exploring the relationship between long-term inhalation exposure to $PM_{10-2.5}$ and changes in BP. Since the publication of that review, a toxicological study has reported no changes in mRNA levels of angiotensin or bradykinin related genes after long-term exposure to $PM_{10-2.5}$ (Aztatzi-Aguilar et al., 2015). However, the authors did report an increase in AT_1R protein levels following exposure ($p < 0.05$). Thus, there is limited evidence from this study that exposure to $PM_{10-2.5}$ may effect BP through changes in the renin-angiotensin system. More information on this recently published study can be found in Table 6-68 below.

Table 6-68 Study-specific details from toxicological studies of long-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 32 µg/m^3 $PM_{10-2.5}$ for 5 h/day, 4 days/week, for 8 week	Angiotensin and bradykinin system gene and protein expression

m = male n = number, h = hour, d = day, week = week

6.4.7 Peripheral Vascular Disease (PVD), Venous Thromboembolism, Pulmonary Embolism

Pulmonary emboli (PE) are common subtypes of venous thromboembolism (VTE) (Section 6.3.8). Pun et al. (2015) reported a positive association between long-term exposure to $PM_{10-2.5}$ and PE [HR: 1.09 (95%CI: 1.00, 1.19)] (Table 6-69). The association was stronger with idiopathic PE, i.e., cases for which there was no underlying medical condition. Although confidence intervals were wider, these associations were not substantially attenuated after adjustment for $PM_{2.5}$.

Table 6-69 Characteristics of the studies examining the association between long-term $PM_{10-2.5}$ exposures and other cardiovascular outcomes.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
(Pun et al., 2015) 11 States, U.S. Follow-up 1992-2008 $PM_{10-2.5}$	NHS	Annual avg estimated using spatiotemporal model at residential address C-V R^2 = 0.63	Mean: 8.2 (SD: 4.2) IQR: 4.6	Self-reported diagnosis of PE confirmed by physician medical record review	Copollutant model: NR Copollutant correlations: NR

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Avg = average, IQR = interquartile range, N, n = number of subjects, NR = not reported, NHS = Nurses' Health Study, PE = pulmonary embolism.

6.4.8 Cardiovascular Mortality

In the 2009 PM ISA, there was limited evidence for an association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality for women, but not for men Chen et al. (2005). Several recent U.S. cohort studies (Table 6-70) examined the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality in occupational cohorts. Puett et al. (2009) examined the association between

long-term $PM_{10-2.5}$ exposure and CHD mortality among a cohort of female nurses in the Nurses' Health Study from 13 states in the northeast and Midwest from 1992 through 2002. Spatio-temporal models were used to assign exposure to $PM_{2.5}$ and PM_{10} and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors observed positive associations with CHD mortality, though the associations were attenuated to below the null value in copollutant models that include $PM_{2.5}$. Using a design similar to that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{10-2.5}$ (derived by subtraction of $PM_{2.5}$ from PM_{10}) exposure and mortality CHD among men enrolled in the Health Professionals cohort. Near null associations were observed for CHD mortality in this cohort.

A pooled-analysis of the European ESCAPE cohort combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014). LUR models were used to assign exposure to $PM_{2.5}$ and PM_{10} and the $PM_{10-2.5}$ concentrations were derived via subtraction. The authors applied a common statistical protocol to data from each of the 22 cohorts, from 13 different European countries, in the first stage of the analysis and combined the cohort-specific effects in a second stage. The authors observed a near-null association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality (Beelen et al., 2014). The strongest association was observed for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.17, 95% CI: 0.90, 1.52), though copollutant models with $PM_{2.5}$ were not reported for this comparison. Using the same exposure models used for the pooled cohort study, Dehbi et al. (2016) assigned $PM_{10-2.5}$ exposure to two British cohort studies that were pooled together to examine CVD mortality. The British cohorts included follow-up between 1989 and 2015, though $PM_{10-2.5}$ exposure estimates were available for 2010-2011. The authors observed a negative association when exposure was considered on the continuous scale, but positive associations for each quartile when exposure was categorized. However, the confidence intervals were wide and overlapping for all of the results, and the inconsistency may indicate generally null results, but instability in the model. In a separate European cohort, Bentayeb et al. (2015) used the CHIMERE chemical transport model to estimate PM_{10} and $PM_{2.5}$, and then subtracted to estimate long-term $PM_{10-2.5}$ exposure. The authors observed positive association with cardiovascular mortality.

While there are more studies available in this review that examine the association between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality, the body of evidence remains limited, especially when compared to the body of evidence available for $PM_{2.5}$. In addition, to date all of the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates. Overall, there is no consistent pattern of associations for cardiovascular mortality (Table 11-8). In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$.

Table 6-70 Epidemiologic studies of long-term exposure to $PM_{10-2.5}$ and cardiovascular mortality.

Study	Cohort (Location)	Mean $PM_{10-2.5}$ ($\mu g/m^3$)	Exposure Assessment	Single Pollutant Hazard Ratio[a] (95% CI)	Copollutant Examination
Chen et al. (2005)	AHSMOG (U.S.)	25.4	ZIP code average Subtraction method	CHD (men): 0.96 (0.81, 1.14) CHD (women): 1.17 (0.98, 1.40)	Correlation (*r*): NA Copollutant models with: NA
†Puett et al. (2009)	Nurses Health (U.S.)	7.7	Spatio-temporal models Subtraction method	CHD (women): 1.07 (0.85, 1.33)	Correlation (*r*): NA Copollutant models with: $PM_{2.5}$: CHD (women): 0.95 (0.75, 1.22)
†Puett et al. (2011)	Health Professionals (U.S.)	10.1	Spatio-temporal models Subtraction method	CHD (men): 1.03 (0.90, 1.18)	Correlation (*r*): NR Copollutant models with: $PM_{2.5}$: CHD (men): 1.05 (0.90, 1.22)
†Beelen et al. (2014)	ESCAPE (Europe)	4.0 – 20.7	LUR models Subtraction method	CVD: 1.02 (0.91, 1.13) IHD: 0.92 (0.77, 1.11) MI: 0.88 (0.71, 1.10) CBVD: 1.17 (0.90, 1.52)	Correlation (*r*): NR Copollutant models with: NR
†Dehbi et al. (2016)	Two British Cohorts	6.4	Same exposure as ESCAPE	CVD: 0.94 (0.56, 1.60)	Correlation (*r*): NR Copollutant models with: NR
†Bentayeb et al. (2015)	Gazel (France)	8.0	CHIMERE chemical transport model Subtraction Method	CVD: 1.32 (0.89, 1.91)	Correlation (*r*): NR Copollutant models with: NR

CHD=coronary heart disease, CVD=cardiovascular disease, ESCAPE = European Study of Air Pollution Exposure, LUR = land use regression, NR=not reported

†Studies published since the 2009 PM ISA.

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6.4.9 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, systemic inflammation and oxidative stress have been linked to a number of CVD related outcomes. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following long-term PM10-2.5 exposures.

6.4.9.1 Epidemiologic Studies

Increased levels of C-reactive protein (CRP) can indicate systemic inflammation (Section 6.3.12) and fibrinogen is a marker of coagulation (Section 6.3.13). (Lanki et al., 2015) provides little support for an association (% difference) between long-term exposure to $PM_{10-2.5}$ and CRP (3.0% [95%CI: -.7, 6.8]) or fibrinogen (1% [95%CI: -1.2, 0.9]).

6.4.9.2 Toxicology Studies

There were no studies in the 2009 PM ISA exploring the relationship between long-term inhalation exposure to $PM_{10-2.5}$ CAP and systemic inflammation/oxidative stress. Since the publication of the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that rats exposed to coarse PM had no change in IL-6 or HO-1 protein levels in the heart following long-term exposure to $PM_{10-2.5}$. More information on this recently published study can be found in Table 6-71 below.

Table 6-71 Study specific details from toxicological studies long-term $PM_{10-2.5}$ exposure and of systemic inflammation.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per group	Inhalation of 32 μg/m^3 $PM_{10-2.5}$ for 5 h/day, 4 days/week, for 8 week	Markers of inflammation in heart tissue collected 24 h post-exposure

Note: n = number, M = male, h = hour, d = day, week = week

6.4.10 Summary and Causality Determination

In the 2009 PM ISA (U.S. EPA, 2009), the evidence describing the relationship between long-term exposure to $PM_{10-2.5}$ and cardiovascular effects was characterized as "inadequate to infer the presence or absence of a causal relationship." The limited number of epidemiologic studies reported contradictory results and animal toxicological evidence demonstrating an effect of $PM_{10-2.5}$ on the

cardiovascular system was lacking. The literature base has expanded but remains limited although some epidemiologic studies report positive associations of cardiovascular mortality and other outcomes with long-term exposure to $PM_{10-2.5}$. More recent evidence describing the relationship between long-term exposure to $PM_{10-2.5}$ and cardiovascular effects is discussed below and summarized in Table 6-72, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

The evidence relating long-term exposure to $PM_{10-2.5}$ to cardiovascular mortality remains limited. Overall, there is no consistent pattern of associations for cardiovascular mortality (Table 6-70). In the instances where positive associations were observed for long-term $PM_{10-2.5}$ exposure and mortality, and $PM_{2.5}$ copollutant model results were reported, the $PM_{10-2.5}$ effect estimates were often attenuated but still positive after adjusting for $PM_{2.5}$. The epidemiologic studies examining the relationship between $PM_{10-2.5}$ and other cardiovascular outcomes including MI and stroke, atherosclerosis, VTE, and blood pressure has grown. Some studies report positive associations with these outcomes. Specifically, single pollutant associations of long-term exposure to $PM_{10-2.5}$ with IHD were observed in the NHS (Hart et al., 2015b), ESCAPE (Cesaroni et al., 2014), and MINAP (recurrent MI) (Tonne et al., 2015) while no association was observed in the HPFU after adjusting for $PM_{2.5}$ in copollutant models (Puett et al., 2011). After adjusting for noise, Hoffmann et al. (2015) reported an inverse association with IHD in the HNR study, which is one of the cohorts included in ESCAPE. Evidence of an association between long-term exposure to $PM_{10-2.5}$ and stroke was similarly inconsistent with a positive association observed in the NHS (Hart et al., 2015b) and little evidence of an effect in HPFU (Puett et al., 2011) or ESCAPE (Stafoggia et al., 2014). No evidence of an association with cIMT in the only available study, an ESCAPE meta-analysis, was reported(Perez et al., 2015). An association between long-term $PM_{2.5}$ exposure and pulmonary embolism was reported in the NHS (Pun et al., 2015). An inconsistent pattern of results relating to the effect of $PM_{10-2.5}$ on increased blood pressure and hypertension was reported in a limited number of studies (Chen et al., 2015a; Fuks et al., 2014). To date the studies that have examined the relationship between long-term $PM_{10-2.5}$ exposure and mortality have used the difference method to derive concentrations for $PM_{10-2.5}$, contributing to the uncertainty associated with these effect estimates.

The toxicological evidence related to long-term $PM_{10-2.5}$ exposures was overall lacking and represents a substantial data gap in the present collection of literature. There was a study demonstrating that short-term $PM_{10-2.5}$ exposure in rats resulted in thickening of the coronary artery wall (Section 6.4.3.2). The same study also reported limited evidence of altered protein expression related to renal function and blood pressure, (Section 6.4.6.2) and no evidence for changes in markers of systemic inflammation or oxidative stress (Section 6.4.9). In addition, as evidenced in Section 6.4.1, there are important gaps in biological plausibility in part, due to the overall lack of experimental evidence.

There are individual high-quality epidemiologic studies that report positive associations with cardiovascular morbidity and mortality outcomes, but the evidence in not entirely consistent. Associations are sometimes attenuated in copollutant models and there is uncertainty stemming from the use of the subtraction method to estimate exposure. Furthermore, evidence from experimental animal studies is of

insufficient quantity to establish biological plausibility. Based largely on the observation of positive associations in some high-quality epidemiologic studies, the **evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cardiovascular effects.**

Table 6-72 Summary of evidence indicating that the evidence is suggestive of, but not sufficient to infer a causal relationship between long-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Some epidemiologic studies report positive associations at relevant concentrations	Positive associations between long-term $PM_{10-2.5}$ exposure and cardiovascular mortality in some studies; however, lack of consistency across studies. Some high-quality studies report associations with IHD, stroke, or pulmonary embolism	Section 6.5.138 (Hart et al., 2015b) Cesaroni et al. (2014) Tonne et al. (2015) Pun et al. (2015) Miller et al. (2007)	8.7 7.3-31 8.2-8.6
Uncertainty regarding exposure measurement error	Studies rely on subtraction method to estimate exposure to $PM_{10-2.5}$ adding uncertainty to the interpretation of effect estimates	Section 3.5	
Uncertainty regarding the independent effect of $PM_{10-2.5}$	Limited number of epidemiologic studies evaluate copollutant confounding Null association with IHD after adjustment for $PM_{2.5}$ in HPFU Inverse association with IHD in HNR study after adjustment for noise	Puett et al. (2011) Hoffmann et al. (2015)	
Limited evidence of coherence across lines of evidence	A study reporting some indications of impaired heart function, and potentially changes in BP. No changes in markers of inflammation or oxidative stress were reported	(Aztatzi-Aguilar et al., 2015)	~30 µg/m^3

Table 6-72 (Continued): Summary of evidence indicating that the evidence is suggestive of, but not sufficient to infer a causal relationship between long-term $PM_{10-2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Biological plausibility	Overall, biological plausibility is extremely limited with important gaps in the potential pathways identified in Section 6.4.1.		

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal diameter of 2.5 μm

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

6.5 Short-Term UFP Exposure and Cardiovascular Effects

The 2009 ISA concluded the available evidence for short-term ultrafine particle (UFP) exposure and cardiovascular effects was "suggestive of a causal relationship." There was a relatively large body of evidence from controlled human exposure studies of fresh diesel exhaust (DE), which is typically dominated by UFPs, demonstrating effects of UFP on the cardiovascular system. In addition, cardiovascular effects were demonstrated by a limited number of laboratories in response to UF carbon black, urban traffic particles and CAPs. Responses included altered vasomotor function, increased systemic oxidative stress and HRV parameters. Studies using UF CAPs, as well as wood smoke and DE, provided some evidence of changes in markers of blood coagulation, but findings were not consistent. Toxicological studies conducted with UF TiO_2, CB, and DE demonstrated changes in vasomotor function as well as in HRV. Effects on systemic inflammation and blood coagulation were less consistent. PM-induced cardiac oxidative stress was noted following exposure to gasoline exhaust. Notably, the few epidemiologic studies of UFPs conducted did not provide strong support for an association of UFPs with effects on the cardiovascular system.

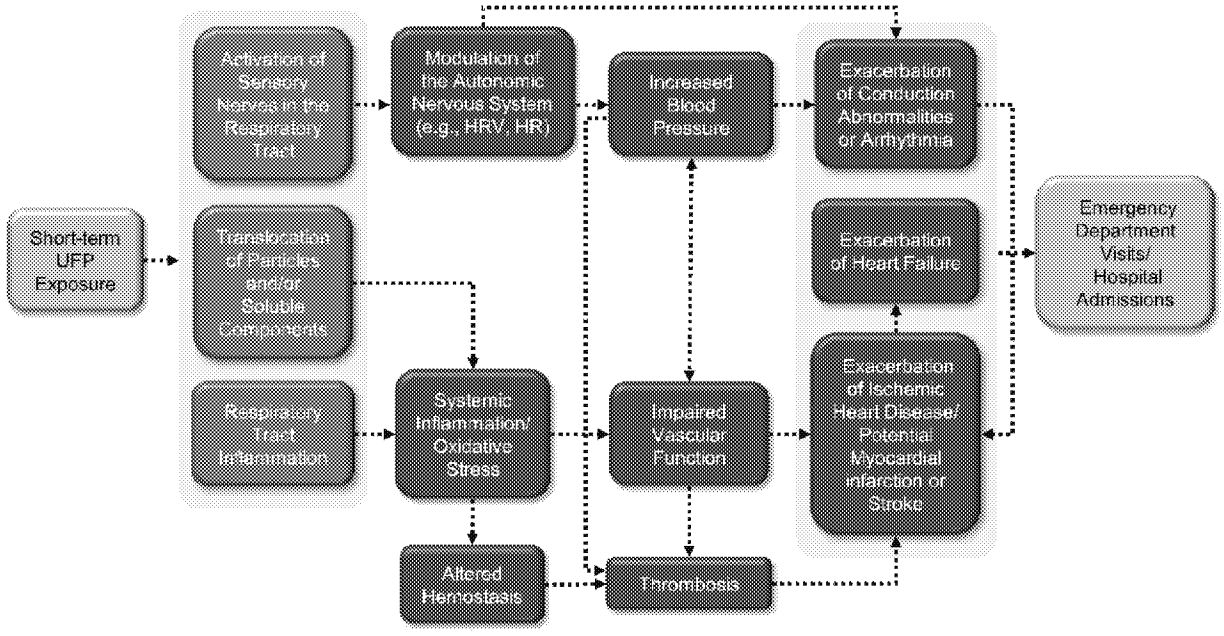
Recent evidence continues to be suggestive of a causal relationship between short-term exposures to UFPs and cardiovascular effects. Relatively speaking, the strongest evidence for cardiovascular-related effects following UFP exposure is for measures of HRV and coagulation. A small number of epidemiologic panel studies have reported associations between short-term exposure to UFPs and measures of HRV. This includes a well conducted epidemiologic panel study that found increases in SDNN with well-characterized 3 hour exposures. In addition, there was some evidence for positive

associations between UFP exposure and markers of coagulation from epidemiologic panel studies, and evidence from a CHE study indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in a subset of individuals with metabolic syndrome who express the GSTM1 null allele. In addition to changes in HRV and markers of coagulation, there was also limited evidence from CHE and epidemiologic panel studies for endothelial dysfunction, blood pressure, and systemic inflammation following UFP exposure.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-short-term UFP exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term UFP exposure (Section 6.5.1). Following this discussion, the health evidence relating short-term UFP exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.5.2), heart failure and impaired heart function (Section 6.5.3) cardiac electrophysiology and arrhythmia (Section 6.5.4), cerebrovascular disease and stroke (Section 6.5.5), increased blood pressure and hypertension (Section 6.5.6), aggregated cardiovascular outcomes (Section 6.5.7), and cardiovascular-related mortality (Section 6.5.8). The evidence for an effect of UFP exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.5.9, Section 6.5.10, Section 6.5.11, and Section 6.5.12). Finally, considering the all of the information presented above, summary and causal determinations are presented (Section 6.5.13).

6.5.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from short-term inhalation exposure to UFPs. Figure 6-36 graphically depicts these proposed pathways as a continuum of pathophysiological responses- connected by arrows- that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies (i.e., ED visits and hospital admissions). This discussion of "how" short-term exposure to UFPs may lead to these cardiovascular events also provides at least some biological plausibility for the epidemiologic results reported later in Section 0. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 0.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-36 Potential biological pathways for cardiovascular effects following short-term exposure to ultrafine particle (UFP).

When considering the available health evidence, plausible pathways connecting short-term exposure to UFPs to the apical events reported in epidemiologic studies are proposed in Figure 6-36. The first pathway begins as respiratory tract inflammation that leads to systemic inflammation[67]. The second pathway involves activation of sensory nerve pathways in the respiratory tract that leads to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to UFPs may result in a series of pathophysiological responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and HF.

Short-term inhalation exposure to UFPs may result in respiratory tract inflammation (CHAPTER 5). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter the circulatory system where they may cause distal pathophysiological responses that contribute to overt cardiovascular disease (see Section 6.1.1). There is limited evidence from CHE studies that following

[67] It is also possible that UFP or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

short-term UFP exposure, systemic inflammation (Liu et al., 2015a; Devlin et al., 2014) may occur. Importantly, systemic inflammation may result in altered hemostasis which may then increase the potential for thrombosis and possibly worsen IHD and HF. In addition, systemic inflammation may result in impaired vascular function that could potentially lead to rupture of existing plaques (Halvorsen et al., 2008). Dislodged plaques may then obstruct blood flow to the heart or stimulate intravascular clotting (Karoly et al., 2007), both of which could result in worsening of IHD and set the stage for HF. Thus, it is important to note that there is some evidence from CHE (Devlin et al., 2014) and epidemiologic panel studies (Wang et al., 2016; Rich et al., 2012; Hildebrandt et al., 2009; Peters et al., 2009) for altered hemostasis following short-term UFP exposure. Similarly, a CHE (Devlin et al., 2014) and an epidemiologic panel study (Ljungman et al., 2014) provide some evidence for impaired vascular function.

There is also evidence that short-term exposure to UFPs could potentially lead to these outcomes through activation of sensory nerves in the respiratory tract (CHAPTER 5). Once activated, autonomic nervous system modulation could exacerbate IHD and HF through proposed pathways that include increases in BP and/or exacerbation of conduction abnormalities or arrhythmia (Figure 6-36). Thus, it is important to note that CHE (Devlin et al., 2014; Samet et al., 2009) and epidemiologic panel studies (Hampel et al., 2014; Rich et al., 2012) report modulation of the autonomic nervous system (as evidenced by changes in HRV) following short-term UFP exposure. Similarly, evidence for increases in blood pressure can be found in epidemiologic panel studies (Chung et al., 2015; Kubesch et al., 2014; Liu et al., 2014b; Weichenthal et al., 2014a), while CHE (Devlin et al., 2014; Samet et al., 2009) and an additional epidemiologic panel (Link et al., 2013) study report conduction abnormalities or indicators of arrhythmia following short-term UFP exposure.

When considering the available evidence, there are potential pathways connecting short-term exposure to UFPs to cardiovascular health effects (Figure 6-36). More specifically, there exist potential pathways by which short-term exposure to UFPs may worsen IHD or HF, as well as contribute to the development of MI or stroke, potentially resulting in ED visits and hospital admissions. That said, the evidence supporting most of the individual events in these potential pathways is quite limited. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.5.13).

6.5.2 Ischemic Heart Disease and Myocardial infarction

As noted above in Section 6.1.2, ischemic heart disease (IHD) is characterized by reduced blood flow to the heart. The majority of IHD cases are caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restrict of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack occurs as a consequence of IHD, resulting in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms and leads to muscle tissue death.

There was no evidence in the 2009 PM ISA with respect to IHD, MI and short-term exposure to UFPs. In the current review, there are a few ED visit and hospital admission studies as well as a single epidemiologic panel study. Overall these studies do not suggest a relationship between short-term exposure to UFPs and IHD or MI.

6.5.2.1 Emergency Department Visits and Hospital Admissions

In Rome, Italy, Belleudi et al. (2010) considered nearly 23,000 ED visits for acute coronary syndrome and observed null associations with UFP exposure (particle number concentrations from a single, fixed-site monitor) at individual lags from 0 to 6 days. Gardner et al. (2014) also reported a null association between two subtypes of MI (ST segment elevation MI and non-ST segment elevation MI) and UFP (particle number concentration, 10-100 nm, from a fixed-site monitor) in a MI registry study in Rochester, NY. Conversely, in a MI registry study in Augsburg, Germany, Wolf et al. (2015a) observed a positive, albeit imprecise (i.e., wide 95% CI), association between same-day UFP exposure (particle number concentration, 10-2000 nm, from a fixed-site monitor) and MI. Additionally, Wolf et al. (2015a) observed a positive increase in recurrent MI events with UFP exposure averaged over a longer, multiday lag period (6.0%, 95% CI: 0.6%, 11.7%, lag 0-4 per 6,800 particles/cm^3 increase). Registry studies are advantageous because they are thought to lessen the degree of outcome misclassification generally seen in studies that rely on administrative data.

6.5.2.2 Panel Epidemiologic Studies of ST Segment Depression

There were no studies evaluating ST-segment depression available for the 2009 ISA and there is only a singly study in the recently published literature. Delfino et al. (2011) conducted a repeated measures study among older adults with coronary artery disease living in retirement communities in Los Angeles and did not find evidence for associations between average PNC of 1-hour up to 4-days and ST-segment depression.

6.5.3 Heart Failure and Impaired Heart Function

As first noted in Section 6.1.3, heart failure (HF) refers to a set of conditions including congestive heart failure (CHF) in which the heart's pumping action is weakened. With CHF the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues.

There were no studies in the 2009 PM ISA with respect to short-term UFP exposure and heart function. In the current review, a hospital admission study showed a positive association that was lag

dependent. However, relative to control animals, a toxicological study did not find an increase in markers consistent with cardiac damage following short-term exposure to $PM_{10-2.5}$.

6.5.3.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for heart failure. Recently, Belleudi et al. (2010) reported positive associations between ambient UFP exposure (particle number concentration from a single fixed-site monitor) and hospital admissions for heart failure in Rome, Italy. The authors examined individual lags from 0 to 6 days, and observed the highest magnitude associations at lag 0 (1.80% [95% CI: 0.39, 3.24%] per 9,392 particles/cm^3 increase) and lag 2 (1.65% [95% CI: 0.32, 3.00%]), with null associations at lags 5 and 6.

6.5.3.2 Toxicology Studies of Impaired Heart Function

There were no animal toxicological studies in the last review examining markers of potential heart failure following short-term UFP exposure. Since that document, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in LVDP or contractility. In addition, (Aztatzi-Aguilar et al., 2015) did not report statistically significant cardiac gene expression consistent with cardiac damage following short-term exposure to UFPs. More information on this recently published study can be found in Table 6-73 below.

Table 6-73 Study specific details from toxicological studies of short-term UFP exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of UFP (107 $\mu g/m^3$) for 5 h/day, for 3 days	Acta1 and Col3a gene expression
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 $\mu g/m^3$ UFP for 4 h	LVDP and contractility (dP/dt) Tissue collected 24h post exposure.

Note: d = day, h = hour, n = number, f = female, M = male, LVDP = left ventricular developed pressure, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha, post = post exposure

6.5.4 Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest

Electrical activity in the heart is measured using electrocardiography (ECG). The pattern of depolarization and repolarization in the heart can indicate various forms of arrhythmia and distinguish those arising in the ventricle from those arising in the atria. See Section 6.1.4 for more information on arrhythmia and measures of conduction abnormalities.

The 2009 PM ISA had a single epidemiologic study of ambient UFPs and arrhythmia-related ED visits and HA. In addition, there was a single CHE study that reported a shortening of the QT interval following short-term exposure to UFPs. Since the last review, one epidemiologic study reported a null association for arrhythmia related hospital admissions, but a CHE study did report conduction abnormalities by ECG that could indicate the potential for increased risk of arrhythmia following short-term UFP exposure.

With respect to OHCA, one study in the 2009 PM ISA that found a positive association between short-term UFP exposure and OHCA. Since the 2009 PM ISA, no new studies of OHCA have been reviewed.

6.5.4.1 Emergency Department Visits and Hospital Admissions for Arrhythmia and Out-of-Hospital Cardiac Arrest

A number of studies based on administrative databases have sought to evaluate the association between short-term fluctuations in ambient UFP concentrations and the risk of hospitalization for cardiac arrhythmias (also known as dysrhythmias). In these studies, a primary discharge diagnosis of ICD-9 427 has typically been used to identify hospitalized patients. ICD-9 427 includes a heterogeneous group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoatrial node dysfunction.

The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and arrhythmia-related ED visits and HA. Recently, Anderson et al. (2010) examined the association between UFP exposure (particle number concentration, single fixed-site monitor) and atrial fibrillation in London, England. The authors reviewed records of implantable cardioverter defibrillators activations and reported a null association with UFP (OR: 1.00, 95% CI: 0.96, 1.05, per 1,000 particles/cm^3 increase, lag 0-5).

The majority of out-of-hospital cardiac arrests are due to cardiac arrhythmias. The 2009 PM ISA reviewed one study examining the association between UFP and OHCA. A study in Rome, Italy (Forastiere et al., 2005) reported positive associations between OHCA and UFPs. No studies published since the release of the 2009 PM ISA examined the association between UFP concentrations and OHCA.

6.5.4.2 Panel Epidemiologic Studies for Arrhythmia and Conduction Abnormalities

In the 2009 PM ISA, (Dockery et al., 2005b) reported a positive association for arrhythmias relative to 2-day averages of UFP. A handful of studies examined the relationship between short-term exposure to UFPs and changes in arrhythmia or cardiac conduction and generally reported null results. While Link et al. (2013) found a positive association between arrhythmia and 2-hour averages of NCs measured at the clinic site in a panel of adults with ICDs, null associations were reported for 24-hour averages. Positive associations for ventricular tachyarrhythmia with NCs in the prior 24-47 hours (0.5%; 95% CI: -0.1, 1.0; per 7,481/cm^3) were also reported by Bartell et al. (2013) in a study of ventricular tachyarrhythmia in older adults with coronary artery disease that used residential monitoring for NC (100-3,000nm); however, negative associations were reported with NCs in the prior 96-119 hours (-0.6%; 95% CI: -1.3, 0.1; per 7,481/cm^3) Hampel et al. (2010) and Rich et al. (2012) both examined QTc changes in relation to ambient NCs (10-100nm) among survivors of MI and cardiac rehabilitation patients, respectively. Hampel et al. (2010) used fixed site monitoring representative of urban background NCs in Dusseldorf, Germany. (Rich et al., 2012) conducted monitoring at the clinic site in Rochester, NY, located roughly 1,500 m from an interstate highway and within 19km of study participants. Neither study reported evidence of associations with 5-hour up to 5-day NC averages.

6.5.4.3 Controlled Human Exposure Studies for Arrhythmia and Conduction Abnormalities

In the 2009 ISA, a CHE study examined the relationship between ultrafine PM exposure and ventricular arrhythmia. Samet et al. (2009) reported a shortened QT interval. They also noted increased variance in the duration of QRS complexes under ultrafine CAP exposure in healthy, young individuals.

In the current ISA, an additional study examined the relationship between UFP CAP exposure and potential indicators of ventricular arrhythmia. Devlin et al. (2014) recently studied adults with metabolic syndrome, including a subgroup with the null allele for glutathione S-transferase (GSTM1- an important antioxidant gene). The GSTM1 null allele individuals had a small but significant increase in the QT interval one-hour post exposure ($p = 0.0070$) relative to FA, while a nonsignificant trend in increased QTc was reported for the entire study group. These GSTM1 null individuals also had an increased complexity of the QRS complex (possible indicator of increased risk of arrhythmia development) at both one-hour ($p = 0.025$) and 20 hours ($p = 0.008$) post exposure. More information on studies published since the 2009 ISA can be found in Table 6-74 below.

Table 6-74 Study-specific details from CHE studies of short-term UFP exposure and conduction abnormalities.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UFPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Measures of conduction abnormalities including QT interval: from continuously worn halter data

Note: SD = standard deviation, M = male, F = female, n = number, GSTM1 = Glutathione S-transferase Mu 1, ECG = electrocardiogram QT = time interval between from beginning of the Q-wave to end of the T-wave

6.5.4.4 Toxicological Studies for Arrhythmia and Conduction Abnormalities

In the 2009 ISA, there were no toxicological studies that examined the effect of UFP CAP exposure on indicators of arrhythmia or conduction abnormalities. In the current review, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in ECG measurements. More information on this recently published study can be found in Table 6-75 below.

Table 6-75 Study specific details from toxicological studies of short-term ultrafine particle (UFP) exposure and conduction abnormalities.

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 µg/m^3 UFP CAP for 4h.	QRS, QT interval, *P*-wave,

d = day, h = hour, n = number, f = female, M = male, ECG = electrocardiogram, QT = time interval between from beginning of the Q-wave, to end of the T-wave, c = corrected for heart rate

6.5.5 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries. Ischemic stroke results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction. Hemorrhagic stroke is less common but results to a disproportionate amount of fatalities.

There were no studies in the last review with respect to short-term UFP exposure and stroke. The current review has a single hospital admission study that generally found a positive association between short-term UFP exposure and stroke.

6.5.5.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA did not review any epidemiologic studies of UFP concentrations and ED visits and hospital admissions for CBVD/stroke. Andersen et al. (2010) recently studied 7,485 incident hospital admissions for stroke in Copenhagen, Denmark from 1995 to 2003. Data from a national stroke registry allowed the authors to consider stroke type (ischemic vs. hemorrhagic), stroke severity (mild vs. severe), and ischemic stroke subtype (with atrial fibrillation vs. without atrial fibrillation) in relation to UFP exposure (particle number concentration (10-700 nm) measured by fixed-site monitors at two urban locations). Andersen et al. (2010) observed increases in odds of hospital admissions for ischemic stroke, mild stroke, ischemic stroke without atrial fibrillation, and mild ischemic stroke without atrial fibrillation over the previous five days (lag 0-4). The associations were generally imprecise (i.e., wide 95% CIs), especially for the subgroup analyses. The association with the highest magnitude was observed between UFP exposure and hospital admissions for mild ischemic stroke without atrial fibrillation (OR: 1.21, 95% CI: 1.04, 1.41, per 3,918 particles/cm^3 increase, lag 0-4). The observed association was robust to adjustment for PM_{10}, NO_X, and CO in copollutant models.

6.5.6 Blood Pressure and Hypertension

High blood pressure results in the increased force on the artery walls and can damage the blood vessels and increase risk for cardiovascular disease and stroke. Hypertension is characterized by persistently elevated blood pressure. Additional information on blood pressure and hypertension can be found in Section 6.1.6.

In the 2009 PM ISA, a handful of epidemiologic panels studies and a single CHE study reported that exposure to UFPs did not result in increases in BP. In the current review, an additional CHE studies also reported that exposure to UFPs did not result in increases in BP. However, panel epidemiologic studies in the current review do provide some evidence for increases in blood pressure following UFP exposure. Thus, across disciplines evidence is both limited and inconsistent.

6.5.6.1 Emergency Department Visits and Hospital Admissions

Hypertension, a medical condition characterized by persistently elevated blood pressure, is a leading risk factor for myocardial infarction, heart failure, and cerebrovascular diseases. The 2009 PM

ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for hypertension. In the only recent study available, Franck et al. (2011) observed positive associations between short-term UFP exposure (measured by particle number concentration, < 100 nm, single fixed-site monitor) and emergency calls for hypertensive crisis in Leipzig, Germany. The authors examined individual lags from 0 to 10 days, and observed positive associations at every lag except for 0, 1, and 10. The authors presented their results graphically; detailed effect estimates were not provided. Additionally, when using alternative exposure metrics based on surface area and volume concentrations, Franck et al. (2011) reported cardiovascular effects were not "significantly correlated" with UFP exposure (quantitative results not presented).

6.5.6.2 Panel Epidemiologic Studies of Changes in Blood Pressure (BP)

Limited evidence was available for the 2009 PM ISA (U.S. EPA, 2009) examining exposures to UFP and changes in BP, though several recently published studies are available. Weichenthal et al. (2014a), Kubesch et al. (2014), and Liu et al. (2014b) all conducted studies that were quasi-experimental in design and provide some evidence for associations between $PM_{2.5}$ and SBP and DBP. Weichenthal et al. (2014a) and Liu et al. (2014b) both used personal monitoring for NCs (10-100nm) with differential exposure scenarios (sites with high and low pollution). Weichenthal et al. (2014a) reported positive associations between 2-hour averages of NCs with SBP measurements taken 3 hours post-exposure, but associations with SBP were null. In contrast, Liu et al. (2014b) reported a decrease in DBP and NCs with a 1-day lag (-0.78 mm hg; 95% CI: -1.40, -0.16; per 10256/cm^3). Chung et al. (2015) and Kubesch et al. (2014) both utilized differential exposures to traffic. Kubesch et al. (2014) measured SBP and DBP in participants following a 2 hour exposure to high or low traffic and found positive associations personal average NCs (100-1000nm) and SBP, but not DBP. Chung et al. (2015) also included participants with differential traffic exposures and reported positive associations between NC and SBP, but not DBP, though there is greater uncertainty in NCs in this study do to fixed-site monitoring. Rich et al. (2012) also examined associations between BP and exposures to UFPs in a panel of cardiac rehabilitation patients that lived within 19 km of the clinic where NCs (10-100 nm) were measured. Associations between NCs and DBP were positive across exposure periods ranging from 23-hours up to 4-days, though a decrease in DBP was associated with 5-day averages of NCs; positive associations were also observed for SBP with 1- to 5-day average NCs (Rich et al., 2012). Overall, these recent studies provide some evidence of a relationship between exposure UFPs and BP that is in contrast to evidence for exposures to $PM_{2.5}$, but the evidence base is still quite small for UFP exposures compared to $PM_{2.5}$.

6.5.6.3 Controlled Human Exposure Toxicology Studies of Changes in Blood Pressure (BP)

In studies from the 2009 ISA, BP was not found to be affected by exposure to UF carbon particles (Frampton, 2001), UF EC (Shah et al., 2008; Routledge et al., 2006), or UF ZnO (Beckett et al., 2005). In the current ISA, no changes in BP were reported by Devlin et al. (2014) in metabolic syndrome patients (including those with GSTM1 null allele) exposed to UFP CAPs. In addition, in healthy men, Mills et al. (2011) found an increase in BP following exposure to DE (Table 6-76), however the increase was not attenuated following exposure to particle-filtered DE. Thus, there is no evidence from CHE studies to suggest an effect of UFP exposure on BP. More information on studies published since the 2009 ISA can be found in Table 6-76 below.

Table 6-76 Study specific details from CHE studies of short-term ultrafine particle (UFP) exposure and blood pressure (BP).

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	BP: pre, during, 1 h post
(Mills et al., 2011)	Healthy M N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-minute rest and cycling intervals during exposure Particle filtered exposures had UFP removed	BP: 6 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, DE = diesel exhaust; GSTM1 = Glutathione S-transferase Mu 1, BP = blood pressure

6.5.6.4 Toxicological Studies of Changes in Blood Pressure (BP)

There were no animal toxicology studies in the 2009 PM ISA exploring the relationship between short-term exposure to UFP and the angiotensin system. Since the publication of that review, a study has reported that short-term exposure to UFP can result in statistically significant increases in Ace and B1r, but not At1r mRNA in rat heart tissue (Aztatzi-Aguilar et al., 2015). However, in mice Kurhanewicz et al.

(2014) reported that short-term exposure to UFPs resulted in no appreciable change in Ace serum levels compared to filtered air exposure. More information on these studies can be found in Table 6-77 below.

Table 6-77 Study specific details from toxicological studies of short-term ultrafine particle (UFP) exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of UFP 107 $\mu g/m^3$ for 5 h/day, for 3 days	Renin-angiotensin gene expression. Heart tissue harvested 24 h post exposure
(Kurhanewicz et al., 2014)	Adult, female C57BL/6 mice (10-12 weeks), n = 5-8/group	Inhalation of 138 $\mu g/m^3$ UFP for 4 h	ACE serum levels 24-h post exposure.

Note: d = day, h = hour, n = number, f = female, M = male, ACE = angiotensin converting enzyme

6.5.7 Emergency Department Visits and Hospital Admission Studies of Cardiovascular-Related Effects

Many epidemiologic studies consider the composite endpoint of ED visits and hospital admissions for all cardiovascular diseases, including diseases of the circulatory system. This endpoint generally encompasses ED visits and hospital admissions for ischemic heart disease, MI, PVD, heart failure, arrhythmia, CBVD and stroke, and diseases of pulmonary circulation. A smaller body of studies examine the endpoint of cardiac diseases, a subset of CVD that specifically excludes hospitalizations for cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. The 2009 PM ISA did not review any epidemiologic studies of ambient UFPs and ED visits and hospital admissions for CVD or cardiac disease. Several recent studies are available for review provide emerging evidence of an association between UFP concentrations and ED visits and hospital admissions for CVD.

In a study in London, England, Atkinson et al. (2010) reported that cardiovascular-related hospital admissions were positively associated with UFP exposure (particle number concentration measured at a single fixed-site monitor for lag 1 and lag 0-1; quantitative results not reported; results presented graphically). In another study in London, England using a single fixed-site monitor, Samoli et al. (2016) reported null associations for cardiovascular-related hospital admissions and UFP exposure (particle number count, upper size limit of 3,000 nm, lag 1). Samoli et al. (2016) also examined associations between UFPs exposure (source apportionment, particle number size distribution, particles < 600 nm). The authors reported positive, but imprecise, associations with UFP linked to urban background

and traffic sources, though not for particles attributed to regional nucleation or secondary particle formation. Similarly, in a study of five cities in Central and Eastern Europe, Lanzinger et al. (2016b) reported null associations for UFP (number count, 100 nm; particle number concentration, 800nm) across individual lags (lag 0 to lag 7) and multi-day averaged lags. In city-specific analyses, results did not substantially differ based on the exposure metric used, and results for UFP (NC100nm) were robust to adjustment for $PM_{2.5}$ or NO_2 both in pooled and city-specific estimates. A delayed association was observed in Beijing, China (Liu et al., 2013). Liu et al. (2013) reported a 7.2% (95% CI: 1.1, 13.7%) increase in cardiovascular-related ED visits corresponding to a 9,040 particle/cm^3 increase in 11-day moving average of UFP concentrations (measured by number concentration, particles 3-100 nm, single fixed-site monitor). Liu et al. (2013) also reported attenuated associations with 2-day moving averages based on number concentration (1.1%, 95% CI: -3.0%, 5.3%; 10,340 particle/cm^3, particles 3-100 nm), particularly Aitken mode particles. In Prague, Czech Republic, Braniš et al. (2010) assessed associations between submicron particles (particles 14.6 to 487 nm) measured from a single fixed-site monitor and cardiovascular-related HA. The authors reported positive associations with nucleation (14.6 to 48.7 nm) and Aitken (48.7 to 205 nm) mode particles, but the highest magnitude associations were observed with accumulation (205 to 487 nm) mode particles (e.g., RR 1.093, 95% CI: 1.019, 1.174, at lag 2 per 1,000 particles/cm^3 increase).

Overall, the evidence provides limited support for the presence of a positive association between UFP exposure and cardiovascular-related ED visits and HA. Evidence for this relationship is provided by a limited number of single-city studies conducted in Europe and Asia. The observed associations tend to be for delayed lags, with weak or null associations with UFP concentrations on the same day, and increasing associations thereafter; however, these studies relied on a single monitor to estimate UFP exposure. As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source. The range in measures used to represent UFP exposures also complicates the overall interpretation of results. Furthermore, the studies did not examine the potential for copollutant confounding.

6.5.8 Epidemiologic Studies of Cardiovascular Mortality

In the 2009 PM ISA, a small number of studies examined associations between short-term UFP exposure and cardiovascular mortality, providing some initial evidence of a positive association. Although the number of studies has increased, the total body of evidence remains small, as detailed in CHAPTER 11 (Section 11.4.1). Across studies that examined the UFP – cardiovascular mortality relationship, there is inconsistency in the particle size distribution that was used to represent UFP exposures with some studies measuring total number concentration (NC), while other studies measured NC with the upper end of the size distribution ranging from 100 – 3,000 nm. This disparity in the measurement of UFPs between studies complicates the overall interpretation of results.

The assessment of the relationship between short-term UFP exposure and cardiovascular mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016) and China (Breitner et al., 2011). Focusing on NC, Breitner et al. (2011) reported evidence of a positive association, but confidence intervals were wide, whereas, the other studies evaluated reported no evidence of an association. Additionally, of the studies evaluated, (Breitner et al., 2011) also examined alternative exposure metrics, surface area concentration (SC) and mass concentration (MC), and reported positive associations that were imprecise (SC: 0.24% [95% CI: -2.72, 3.29], lag 0-4 per 12,060 cm^{-3}; MC: 0.13% [95% CI: -2.87, 3.23], lag 0-4 per 14.0 $\mu g/m^{3)}$. Although there is some evidence of a positive association between short-term UFP exposure and cardiovascular mortality, within each study only a single monitor was used to estimate exposure to UFPs (Table 11-9, UFP studies in mortality chapter). As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source.

6.5.9 Heart Rate (HR) and Heart Rate Variability (HRV)

Measured by ECG, heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats, and is an indicator of the balance between the sympathetic and parasympathetic arms of the autonomic nervous system. Additional information on HRV and HR can be found in Section 6.1.10.

In the 2009 PM ISA, there were a handful of epidemiologic panel and CHE studies that reported changes in metrics of HRV following short-term UFP exposure. Since the last review, an additional CHE study reported changes in HRV following UFP exposure. In addition to the CHE studies, several epidemiologic panel studies examined potential associations between metrics of HRV and short-term UFP exposure. The results of these studies were inconsistent with some studies showing positive associations while others did not. In addition, a single toxicological study did not find an effect of UFP exposure on HRV measures. Taken together, there is some evidence for an effect of short-term UFP exposure on HRV, but overall the evidence remains inconsistent within and across disciplines.

With respect to heart rate, a CHE and toxicological study did not find that UFP exposure resulted in changes in heart rate.

6.5.9.1 Epidemiologic Panel Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

Limited evidence was available for the 2009 ISA, though some evidence indicated decreases in HRV relative to increases in PNC. Several recently published studies are available that examine associations between UFP concentrations and HRV (Hampel et al., 2014; Weichenthal et al., 2014a;

Bartell et al., 2013; Rich et al., 2012; Schneider et al., 2010). Rich et al. (2012) reported reduced rMSSD and SDNN with 5-hour and 23-hour lagged exposures to NCs (10-100nm) in a panel of adults in a cardiac rehabilitation program living within 19km of the clinic where monitoring was conducted. Weichenthal et al. (2014a) conducted a quasi-experimental study with personal monitoring for NCs (10-100nm) during ambient exposure periods at different sites and reported positive associations between 2-hour averages of NCs with SDNN measured 3 hours post-exposure, but associations with rMSSD were null. Bartell et al. (2013) also found positive associations between SDNN and 5-day averages of NCs in a study of community-dwelling seniors (71 years of age or older) using residential monitoring for particles 100-3,000 nm in size. In contrast, Schneider et al. (2010) did not find associations between rMSSD or HF with NCs measured at a site representing urban background (10-100nm) in a panel of older adults with coronary artery disease. Overall, these recent studies provide some evidence for an association between exposure to UFP and changes in HRV, particularly SDNN among older adults and individuals with a history of cardiovascular disease.

6.5.9.2 Controlled Human Exposure Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

The 2009 PM ISA discussed two studies that examined HRV, but no studies reporting potential changes in HR. Samet et al. (2009) demonstrated that healthy adults exposed to UF CAPs had an increase in both HF and LF frequency domains, but not in time domains. In addition, Gong et al. (2008) reported a small and transient decrease in LF in healthy and asthmatic adults.

Since the 2009 PM ISA, Mills et al. (2011) reported no difference in HR following exposure to DE (Table 6-78), or particle-filtered DE in healthy men. With respect to HRV, Devlin et al. (2014) exposed metabolic syndrome patients, including a subset with the GSTM1 null allele, to UFP CAP or FA. In the subset of patients expressing the GSTM1 null allele, decreases in HF ($p < 0.05$) and an increase in both LF ($p < 0.05$) and the LF/HF ratio ($p < 0.05$) was reported. Taken together, the is limited evidence of an UFP effect on HRV, but not HR. More information on studies published since the 2009 ISA can be found in Table 6-78 below.

Table 6-78 Study specific details from controlled human exposure (CHE) studies of short-term ultrafine particle (UFP) exposure and changes in heart rate (HR) and heart rate variability (HRV).

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	HRV time parameters: collected over 24 h HRV frequency domains: pre, 1 h post, 20 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	HR: 6 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, CAP = concentrated ambient particle, DE = diesel exhaust; IQR = interquartile range, HRV = heart rate variability, GSTM1 = Glutathione S-transferase Mu 1

6.5.9.3 Toxicology Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

Since the publication of the 2009 ISA, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs resulted in no appreciable change in HR, SDNN, rMSSD, or LF/HF in mice. More information on this recently published study can be found in Table 6-79 below.

Table 6-79 Study specific details from toxicological studies of short-term UFP exposure and heart rate (HR) and heart rate variability (HRV).

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, F C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 µg/m^3 UFP for 4h.	HR, HRV time and frequency domains

n = number, h = hour, d = day, M = male, F = female HR = heart rate, HRV = heart rate variability.

6.5.10 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, inflammation has been linked to a number of CVD related outcomes. For example, circulating cytokines such as IL-6 can stimulate the liver to release inflammatory proteins and coagulation factors that can ultimately increase the risk of thrombosis and embolism. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and a further increase in the inflammatory response. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following short-term UFP exposures.

6.5.10.1 Epidemiologic Panel Studies of Systemic Inflammation and Oxidative Stress

Several recently published panel studies add to the limited evidence available for the 2009 ISA that provide some evidence for increases in systemic inflammation relative to UFP counts. In a panel study including 31 young, healthy adults exposed to air pollution at 5 different sites with intermittent exercise, Steenhof et al. (2014) reported mixed results for associations between UFPs and WBC counts; while decreases were observed for eosinophils and lymphocytes with PNCs at 2 and 18 hours post-exposure, respectively, increases in monocytes were observed and no changes were reported for neutrophils or total WBC counts. In this same panel, no associations were observed for PNC and CRP (Strak et al., 2013a).

In nursing home residents in Los Angeles, CA with ischemic heart disease, Wittkopp et al. (2013) did not find associations for CRP or soluble receptor for IL-6 with up to 5-day averages of PNC. In addition, other studies in panels with pre-existing cardiovascular disease generally did not find evidence for associations. While Rich et al. (2012) and Croft et al. (2017) found a positive association between CRP and 24-47-hour averages of UFPs. Associations were not found for other averaging times or with WBC counts (Rich et al., 2012) and negative associations between 12-96-hour lags of UFPs and myeloperoxidase were observed (Croft et al., 2017). In elderly with ischemic heart disease, PNC was associated with higher IL-12 but not CRP, IL-6, IL1B, IL-8, and IFNγ in 52 participants in Kotka, Finland (Huttunen et al., 2012).

In Heinz Nixdorf Recall study including approximately 4,000 participants, particle number concentration (PNC) based on a chemical transport model with a resolution of 1 × 1 km was associated with higher CRP in averaging periods from 2 up to 28 days with the largest effect estimates reported for 21-day average [7.1% (95% CI 1.9, 12.6) per IQR (4,580 particles x 104/ml)] (Hertel et al., 2010). Similarly, Karottki et al. (2014) reported associations between 48-hour PNC and CRP; no associations were observed for changes in WBCs.

6.5.10.2 Controlled Human Exposure Studies of Short-Term UFP Exposure and Systemic Inflammation and Oxidative Stress

Controlled human exposure studies from the 2009 PM ISA reported no change in plasma CRP levels following a 2-hour exposure to UFPs, although one study looked at and reported a significant increase in IL-8 (Samet et al., 2009; Gong et al., 2008). No change in plasma CRP was reported.

In the current review, Liu et al. (2015a) studied the potential for UFP exposure and endotoxin to associate with the biomarkers for inflammation IL-6 and CRP-. no associations were found. Devlin et al. (2014) also found no differences in sICAM-1 or sVCAM-1 (as well as no differences in neutrophils, lymphocytes, monocytes, platelets) in patients with metabolic syndrome, including a subset with the GSTM1 null allele. However, 20 hour post exposure, CRP was elevated (30.4 ± 11.9%, $p = 0.016$), as was the acute phase inflammatory marker SAA (77.5 ± 37.2%, $p = 0.043$). With respect to filtered diesel exhaust, in healthy men Mills et al. (2011) reported no statistical difference in leukocytes, neutrophils, or lymphocytes following exposure to DE (Table 6-80) or particle-filtered DE. In total, there is limited evidence from one CHE study indicating a systemic inflammatory response in metabolic syndrome patients.

With respect to markers of oxidative stress, Liu et al. (2015a) examined the potential for UF CAP exposure to increase levels of the biomarker of lipid peroxidation MDA and the DNA oxidative damage biomarker 8-OHdG. Ultrafine CAP exposure did not result in an increase in blood or urine levels of MDA. However, urine sampling revealed increases in 8-OHdG (0.69 ng/mg creatinine; 95% CI: 0.09, 1.29) at one hour but not 21 hours post-exposure. Thus, there is only limited evidence to suggest that UFP exposure effects markers of oxidative stress. More information on studies published since the 2009 ISA can be found in Table 6-80 below.

Table 6-80 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and systemic inflammation.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Markers of systemic inflammation and pre,1 h post, 20 h post

Table 6-80 (Continued): Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and systemic inflammation.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Liu et al., 2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	135.8 ± 67.2 µg/m^3 ultrafine cap for 130 min from Toronto, Canada	Markers of inflammation and oxidative stress measured pre, 1 h, and 21 h post
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Markers of coagulation

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

1

6.5.10.3 Toxicological Studies of Short-Term Ultrafine Particle (UFP) Exposure and Systemic Inflammation and Oxidative Stress

2 In the 2009 PM ISA, there were no animal toxicological studies examining the effects of short-
3 term UFP exposure on markers of systemic inflammation or oxidative stress. Since the publication of that
4 document, Kurhanewicz et al. (2014) reported that short-term exposure to UFPs did not result in a change
5 in CRP levels or potential markers of oxidative stress relative to FA control animals. More information on
6 studies published since the 2009 ISA can be found in Table 6-81 below.

Table 6-81 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and systemic inflammation.

Study	Study Population	Exposure Details	Endpoints Examined
(Kurhanewicz et al., 2014)	Adult, F C57BL/6 mice (10-12 week), n = 5-8/group	Inhalation of 138 µg/m^3 UFP for 4h.	CRP, markers of oxidative stress in serum 24h post -exposure

Note: n = number, h = hour, d = day, M = male, F = female CRP = c-reactive protein

6.5.11 Coagulation

Coagulation refers to the process by which blood changes from a liquid to a semi-solid state in order to form a clot. Increases in coagulation factors (e.g., fibrinogen) or decreases in anti-coagulation factors can promote clot formation, and thus, increase the potential for an embolism.

In the 2009 PM ISA, CHE studies examined whether exposure to UFPs could result in changes in markers of coagulation. In general, results from these studies were negative. Since the 2009 PM ISA, a couple of additional CHE studies have reported inconsistent results, with one study showing changes in markers of coagulation, while the other study did not. Similarly, results from epidemiologic panel studies also report limited evidence of an associations between UFP concentrations and changes in markers of coagulation.

6.5.11.1 Panel Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), no studies were available that examined associations between short-term exposure to UFPs and biomarkers of coagulation, though a handful of studies have been published since. Among the recently published studies is one that used a quasi-experimental study design, including personal monitoring at five different locations in Utrecht, the Netherlands allowing for increased exposure contrast and reduced correlations between PM characteristics. Results from this study demonstrate that NCs (7-3000 nm) measured at the five different exposure sites were not associated with platelet counts or fibrinogen (Strak et al., 2013a). However, average NCs for the five-hour exposure periods, particularly those from the outdoor sites, were associated with reduced lag time in FXII-mediated (intrinsic) thrombin generation in a single pollutant model and several two-pollutant models, including those with PM_{10}, $PM_{2.5}$, OC, NO_3-, and SO_4^{2}-. These measures indicated hypercoagulability via the intrinsic pathway, but there was little evidence to suggest changes in the extrinsic pathway (tissue-factor mediated) (Strak et al., 2013b).

Other panel studies have examined fibrinogen and a number of other biomarkers as well. Hildebrandt et al. (2009) conducted a study to examine blood markers in a panel of adults with chronic pulmonary disease and reported positive associations with 1- (2.5%; 95% CI: 0.2, 4.9) and 3-day (2.5%; 95% CI: 0.2, 4.9 and 3.3; 95% CI: 1.0, 5.6, respectively, per 3827/cm^3 increase) lagged NCs (10-100nm) as well as 5-day averages (3.1%; 95% CI: 0.2, 6.0; per 2918/cm^3 increase). However, other study results included a negative association between 3-day lagged NCs and fibrinogen, negative associations between vWF and D-dimer for a number of lags, and null associations for prothrombin fragment 1+2 (Hildebrandt et al., 2009). Fibrinogen was also positively associated with 24- to 47-hour average NCs (10-100nm) in cardiac rehabilitation patients in Rochester, NY (Wang et al., 2016; Rich et al., 2012) and with 12 up to 96 hour averages of NCs (10-100 nm) in adults with acute coronary syndrome (Croft et al., 2017). In contrast, associations with fibrinogen were not observed in a study of older adult participants with

ischemic heart disease (Huttunen et al., 2012) or a panel of individuals with a history of MI (Peters et al., 2009), though exposure measurement, including NC size range, was not described in these studies. Brüske et al. (2011) examined associations between lipoprotein-associated phospholipase A2, which has recently been shown to be an independent predictor of coronary heart disease events, and NCs (<100nm; measured at a fixed-site representing urban background) and found negative associations at 0- to 2-day lags but positive associations for 4-5-day lags in a prospective panel study of MI survivors.

6.5.11.2 Controlled Human Exposure Studies

The 2009 PM ISA included a study of healthy and asthmatic adults exposed to UFP CAPs from CA(Gong et al., 2008). No significant changes were reported for D-dimer, vWF, PAI-1, factors VII and IX, fibrinogen, plasminogen, or TPA levels. In an additional study, healthy adults were exposed to UFPs from NC while alternating between 15-minute rest/exercise sessions. Increases in D-dimer concentration, but not in PAI-1, vWF, tPA, fibrinogen, plasminogen, or factors IX or VII, were found (Samet et al., 2009).

In the current review, Devlin et al. (2014) examined the effects of UFP exposure on markers of fibrinolysis in metabolic syndrome patients, including a subgroup (n = 15) carrying the null allele for GSTM1. The anticoagulant proteins plasminogen ($p = 0.022$) and thombomodulin ($p = 0.048$) had a statistically significant decrease when examining the entire study population at 20 hours but not one hour post exposure. There were no statistically significant changes in a number of other measured markers including tPA, D-dimer, and vWF. Moreover, in healthy men Mills et al. (2011) reported no difference in t-PA and PAI-1 antigen or activity or platelets following exposure to either DE or filtered-DE.

Taken together, there is some evidence from a single CHE study for changes in biomarker levels that would be indicative of increased risk of thrombosis and coagulation in patients with metabolic syndrome. More information on studies published since the 2009 ISA can be found in Table 6-82 below.

Table 6-82 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and coagulation and thrombosis.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Markers of coagulation: pre,1 h post, 20 h post

Table 6-82 (Continued): Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and coagulation and thrombosis.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 μg/m^3 UFP Particles generated with diesel engine passed through 0.1 μm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Markers of coagulation

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

1

6.5.12 Endothelial Dysfunction and Arterial Stiffness

2 Endothelial dysfunction is the physiological impairment of the inner lining of the blood vessels
3 and is typically measured by FMD. Arterial stiffness is associated with a variety of cardiovascular risk
4 factors and outcomes (Laurent et al., 2006) and is best measured by pulse wave velocity (PWV). More
5 information on measures of endothelial dysfunction and arterial stiffness can be found in Section 6.1.13.

6 There were no studies in the 2009 PM ISA examining the relationship between exposure to UFPs
7 and endothelial dysfunction or arterial stiffness. Since publication of the 2009 PM ISA, a single
8 epidemiologic panel and a few CHE studies have examined the potential for UFP exposure to result in
9 changes in measures in endothelial dysfunction. Taken together, these studies provide some evidence that
10 exposure to UFPs can result in endothelial dysfunction.

11

6.5.12.1 Panel Epidemiologic Studies

12 There were no studies in the 2009 ISA examining associations between short-term exposures to
13 UFPs and measures of endothelial dysfunction, and only a single study is available from the recently
14 published literature. Ljungman et al. (2014) examined associations between UFPs and peripheral arterial
15 tonometry, a measure of microvessel dilation, and pulse wave amplitude in the Framingham Heart Study
16 and found positive associations for 1 to 7-day averages.

6.5.12.2 Controlled Human Exposure Studies

In the current review, BAD and FMD were both examined following UFP exposure in metabolic syndrome patients, including a subgroup with the GSTM1 null allele (Devlin et al., 2014). No effects of UFPs were observed following reactive hyperemia or nitroglycerin administration when compared to FA. In contrast, Mills et al. (2011) found that the vasodilation response to bradykinin ($p = 0.005$), acetylcholine ($p = 0.008$), and sodium nitroprusside ($p < 0.001$) were attenuated following exposure to DE (Table 6-83) relative to FA, but not following exposure to particle-filtered DE.

With respect to protein markers of endothelial dysfunction, Liu et al. (2015a) examined whether short-term exposure to UFPs increased levels of and ET-1 or VEGF. There were no increases in blood ET-1 or urine VEGF levels, but the authors did report a statistically significant ($p < 0.05$) increase in blood VEGF levels at 21 hours, but not one hour post exposure.

Taken together, the studies presented above provide some evidence of impaired vasomotor function following short-term exposure to UFPs present in diesel exhaust, but very little evidence following short-term exposure to UFP CAPs. More information on studies published since the 2009 ISA can be found in Table 6-83 below.

Table 6-83 Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and impaired vascular function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Devlin et al., 2014)	Adults with metabolic syndrome n = 13 M; 21 F 27-70, average 15 of which carried the null allele for GSTM1	98 µg/m^3 UF CAPs (73% of which are <0.1 µm) 16,000–564,000 particles/cm^3 for 2 h at rest particles from Chapel Hill, NC	Vascular function: pre, 1 h post, 20 h post
(Liu et al., 2015a)	Healthy adults n = 50; 18-60 yrs 28 ± 9	135.8 ± 67.2 µg/m^3 ultrafine cap for 130 min	Biomarkers of vascular function measured pre, 1 h, and 21 h post

Table 6-83 (Continued): Study specific details from controlled human exposure (CHE) studies of short-term UFP exposure and impaired vascular function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Mills et al., 2011)	Healthy men N = 16 18- 32 yr	300 µg/m^3 UFP Particles generated with diesel engine passed through 0.1 µm filter 15-min rest and cycling intervals during exposure Particle filtered exposures had UFP removed	Vascular function: 6-8 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, GSTM1 = glutathione S-transferase Mu 1, CAP = concentrated ambient particle

1

6.5.13 Summary and Causality Determination

2 In the 2009 PM ISA (U.S. EPA, 2009), the evidence from toxicological studies predominantly
3 using DE exposures was suggestive of a causal relationship between short-term UFP exposure and
4 cardiovascular effects. Cardiovascular effects included altered endothelial function, increased systemic
5 oxidative stress, and altered HRV parameters. In addition, studies using UF CAPs, as well as wood smoke
6 and DE, provided some evidence of changes in markers of blood coagulation, but results were not
7 consistent across studies. The few epidemiologic studies of UFPs in the last review did not provide
8 support for an association of UFPs with effects on the cardiovascular system. More recent evidence
9 describing the relationship between short-term UFP exposure and cardiovascular effects is discussed
10 below and summarized in Table 6-84, using the framework for causality determinations described in the
11 Preamble to the ISAs (U.S. EPA, 2015).

12 Since the publication of the 2009 PM ISA, there have been a limited number of studies describing
13 the relationship between short-term UFP exposure and cardiovascular effects. That being said, there is at
14 least some evidence for cardiovascular effects following short-term exposure to UFPs. A small number of
15 epidemiologic panel studies have observed positive associations between short-term exposure to UFPs
16 and measures of HRV (Section 6.5.9.1) and markers of coagulation (Section 6.5.11.1), although there are
17 also studies that did not report UFP-related effects. In addition, there is evidence from a single CHE study
18 indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in individuals with
19 metabolic syndrome (Section 6.5.11.2). There was also inconsistent evidence from CHE and
20 epidemiologic panel studies for endothelial dysfunction, changes in blood pressure, and systemic
21 inflammation following exposure to UFPs. Notably, there was little evidence of an effect when
22 considering short-term UFP exposure on other cardiovascular endpoints or epidemiologic outcomes such
23 as ED visits or hospital admissions. However, when considered as a whole, the evidence presented in

Section 0 is **suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to UFPs and cardiovascular effects.**

Table 6-84 Summary indicating that evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Evidence from a limited number of epidemiologic panel studies and a controlled human exposure study is generally supportive	Some evidence of positive associations in epidemiologic panel studies of HRV and coagulation A single CHE study indicating decreases in the anticoagulant proteins plasminogen and thombomodulin in individuals with metabolic syndrome.	Section 6.5.10 Section 6.5.11 Section 6.5.12 Section 6.5.13 Devlin et al. (2014)	See tables in identified sections
Limited and inconsistent epidemiologic evidence for ED visits and hospital admissions	Limited evidence does not support association with ED visits and hospital admissions for IHD Limited evidence supports association with ED visits and hospital admissions for aggregate CVD	Section 6.5.2.1 Section 6.5.7	
Uncertainty regarding potential confounding by copollutants	Single study provides limited evidence that UFP association is robust to PM_{10} and gaseous copollutants in study of stroke ED visits. Panel studies did not evaluate potential copollutant confounding	Andersen et al. (2010)	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.		
Uncertainty regarding exposure measurement error	Single study used personal UFP monitoring. Most studies relied on 1 monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Hampel et al. (2014)	
Little evidence from animal toxicological studies	The few animal toxicological studies that examined the relationship between UFP CAP exposure and CVD endpoints reported mostly negative results	(Aztatzi-Aguilar et al., 2015) Kurhanewicz et al. (2014)	

Table 6-84 (Continued): Summary indicating that evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited evidence for biological plausibility of cardiovascular effects	There were very few studies on which to base biologically plausible pathways for the few epidemiologic studies reporting positive associations between UFP exposure and ED visits or hospital admissions	Section 6.5.1 Figure 6-36	

a = Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

b = Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

c = Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

1

6.6 Long-Term UFP Exposure and Cardiovascular Effects

The evidence pertaining to the effect of long-term exposure to ultrafine particles (UFPs) on the cardiovascular system reviewed in the 2009 PM ISA comprised a small number of toxicological studies that indicated the potential for long-term exposure UFP to lead to atherogenic changes. The evidence provided by these studies was characterized as "inadequate to infer the presence or absence of a causal relationship" (U.S. EPA, 2009).

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-term UFP exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-term UFP exposure (Section 6.6.1). Following this discussion, the health evidence relating long-term UFP exposure and specific cardiovascular health outcomes is discussed in detail: atherosclerosis (Section 6.6.2) heart failure and impaired heart function (Section 6.6.3) increased blood pressure and hypertension (Section 6.6.4), and systemic inflammation and oxidative stress (Section 6.6.5). Considering all of the information presented above, summary and causal determinations are then presented (Section 6.6.6).

6.6.1 Biological Plausibility

There continues to be a lack of evidence for health effects following long-term exposure to UFPs. As a result, there is very little evidence for biological plausibility of health effects in humans, and thus, a biological plausibility figure was not constructed for this size fraction. However, as noted below, there is limited toxicological evidence for atherosclerosis (Li et al., 2013), impaired heart function (Aztatzi-Aguilar et al., 2015), systemic inflammation (Aztatzi-Aguilar et al., 2015) and changes in the renin-angiotensin system (Aztatzi-Aguilar et al., 2015).

6.6.2 Atherosclerosis

In the 2009 PM ISA, ultrafine CAPs derived from traffic were demonstrated to increase plaque size in ApoE$^{-/-}$ mice (Araujo et al., 2008). Since the 2009 PM ISA, Aguilera et al. (2016) reported a 2.1% increase (95%CI: 0.03, 4.10) per interdecile increase in PN and 2.3% increase (95% CI: 0.23, 4.4) per interdecile increase in Lung Deposited Surface Area (LDSA). NC (10-300 nm) concentration was measured directly with diffusion classifier for use in LUR model in this study. More information on this recently published study can be found in Table 6-85.

Table 6-85 Characteristics of the epidemiologic study examining the association of UFP with circulating markers of inflammation and coagulation.

Study	Study Population	Exposure Assessment	Concentration	Outcome	Copollutants Examined
†(Aguilera et al., 2016) 4 Cities, Switzerland Cross-sectional PNC: 2011/22 Outcome: 2010/2011	SAPALDIA N = 1,503	2 yr avg estimated at residence using LUR PNC Model R^2 = 0.85 miniature diffusion classifier (10-300 nm)	PNC Mean 11,184 (SD: 4,862) particles/cm^3	cIMT	PNC with $PM_{2.5}$ last yr r = 0.88, $PM_{2.5}$ 2001-2011 r = 0.86; $PM_{2.5}$ vehicular r = 0.86; $PM_{2.5}$ crustal 0.83

LDSA = Lung Deposited Surface Area, PNC = particle number concentration; SAPALDIA = Swiss study on Air Pollution and Lung Disease in adults; Hs-CRP = high sensitivity C-reactive Protein; cIMT = carotid intima media thickness; NR = Not reported

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.6.3 Heart Failure and Impaired Heart Function

Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that long-term UFP exposure in rats resulted in thickening of the coronary artery walls. These authors also found that long-term exposure to UFP resulted in a statistically significant increase in two genes typically associated with cardiac damage in heart tissue: Acta1 and Col3a. Thus, there is limited evidence from animal toxicological studies of potential decreases in heart function following long-term UFP exposure. More information on this study can be found in Table 6-86.

Table 6-86 Study-specific details from toxicological studies of long-term UFP exposure and impaired heart function.

Study	Population N, Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of ultrafine PM (107 µg/m^3) for 5 h/day, 4 days/week, for 8 weeks	Coronary wall thickness, Acta 1 and Col3a1 mRNA

Note: n = number, h = hour, d = day, week = week, M = male, f = female, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.6.4 Blood Pressure and Hypertension

There were no animal toxicology studies in the 2009 PM ISA exploring the relationship between long-term exposure to UFP and the angiotensin system. Since the publication of that review, long term exposure to UFP has been reported to significantly increase mRNA levels in the heart of At2R and At1R ($p < 0.05$), but not Ace, or b1R (Aztatzi-Aguilar et al., 2015). More information on this recently published study can be found in Table 6-87 below.

Table 6-87 Study-specific details from toxicological studies of long-term UFP exposure and blood pressure (BP).

Study	Population N, Sex; Age Mean ± SD	Exposure Details Concentration; Duration	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 107 μg/m^3 ultrafine PM for 5 h/day, 4 days/week, for 8 weeks	Angiotensin and bradykinin system gene and protein expression

m = male n = number, h = hour, week = week

6.6.5 Systemic Inflammation and Oxidative Stress

As discussed in Section 6.1.1 and Section 6.1.11, inflammation has been linked to a number of CVD related outcomes. Similarly, oxidative stress can result in damage to healthy cells and blood vessels and a further increase in the inflammatory response. Thus, this section discusses the evidence for markers of systemic inflammation and oxidative stress following short-term UFP exposures.

6.6.5.1 Epidemiologic Studies

The epidemiologic evidence continues to be limited. In a recent study, Viehmann et al. (2015) observed small longitudinal changes in hs-CRP [3.8 -0.6, 8.4], fibrinogen [1.0 0.0, 2.0], WCC [1.0 -0.1, 2.1] and platelets [0.6 -0.4, 1.7] in association with an IQR increase in 365 day moving average PNC concentration among participants in the HNR study in Germany. The mean PNC concentration was 88,000 in this study.

6.6.5.2 Toxicology Studies

Since the 2009 PM ISA, Aztatzi-Aguilar et al. (2015) reported that rats exposed to UFP had increased ($p < 0.05$) IL-6 and decreased ($p < 0.05$) HO-1 protein levels in heart tissue. More information on this recently published study can be found in Table 6-88 below.

Table 6-88 Study-specific details from toxicological studies of long-term UFP exposure and systemic inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult male Sprague-Dawley rats (n = 4 per group)	Inhalation of 107 μg/m^3 ultrafine PM collected from a high traffic and industrial area north of Mexico City in early summer and exposed for 5 h/day, 4 days/week for 8 weeks	Markers of systemic inflammation and oxidative stress in heart tissue

Notes: m = male n = number, h = hour, d = day, week = week

6.6.6 Summary and Causality Determination

In the 2009 PM ISA, there was evidence from an animal toxicological study of increased atherosclerotic plaque size in mice following long-term exposure to UFPs. Since the publication of the 2009 PM ISA, a small number of epidemiologic studies reporting positive associations between long-term exposure to UFPs and cIMT and markers of inflammation and coagulation have become available. In addition, a single recent animal toxicological study reported evidence of impaired heart function (Section 6.6.3), as well as changes in markers associated with systemic inflammation, oxidative stress (Section 6.6.5.2), and the renin-angiotensin system following long-term UFP exposure (Section 6.6.4). However, the overall toxicological evidence base examining the effects of long-term UFP exposure on cardiovascular endpoints remains extremely limited, and thus, there is little biological plausibility for the effects observed in the epidemiologic studies mentioned above. Therefore, as in the previous review, the evidence characterizing the relationship between long-term UFP exposure and cardiovascular effects is **inadequate to infer the presence or absence of a causal relationship.** The evidence for the relationship between long-term exposure to UFPs and effects on the cardiovascular system is summarized in Table 6-89, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 6-89 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP PM Concentrations Associated with Effects[c]
Limited epidemiologic evidence	Long-term exposure to UFPs associated with Increase in cIMT and markers of inflammation and coagulation; Overall few epidemiologic studies of UFP health effects are conducted.	Aguilera et al. (2016) Viehmann et al. (2015)	Mean: 11,184 particles/cm^3 Mean: 88,000 particles/ml
Limited animal toxicological evidence	Long-term exposure to UFPs increased coronary artery wall thickness, markers of systemic inflammation, and some markers in the renin-angiotensin system.	Aztatzi-Aguilar et al. (2015)	
Uncertainty regarding potential confounding by copollutants	PNC strongly correlated with $PM_{2.5}$ concentrations (r = 0.88)	Aguilera et al. (2016)	
Uncertainty regarding exposure measurement error	Potentially uncharacterized spatial and temporal variation of UFP concentration limits interpretation of epidemiologic evidence		
Uncertainty regarding biological plausibility	Lack of evidence to characterize the biological plausibility of health effects following long-term PM 2.5 exposure.		

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.7 References

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CHAPTER 7 METABOLIC EFFECTS

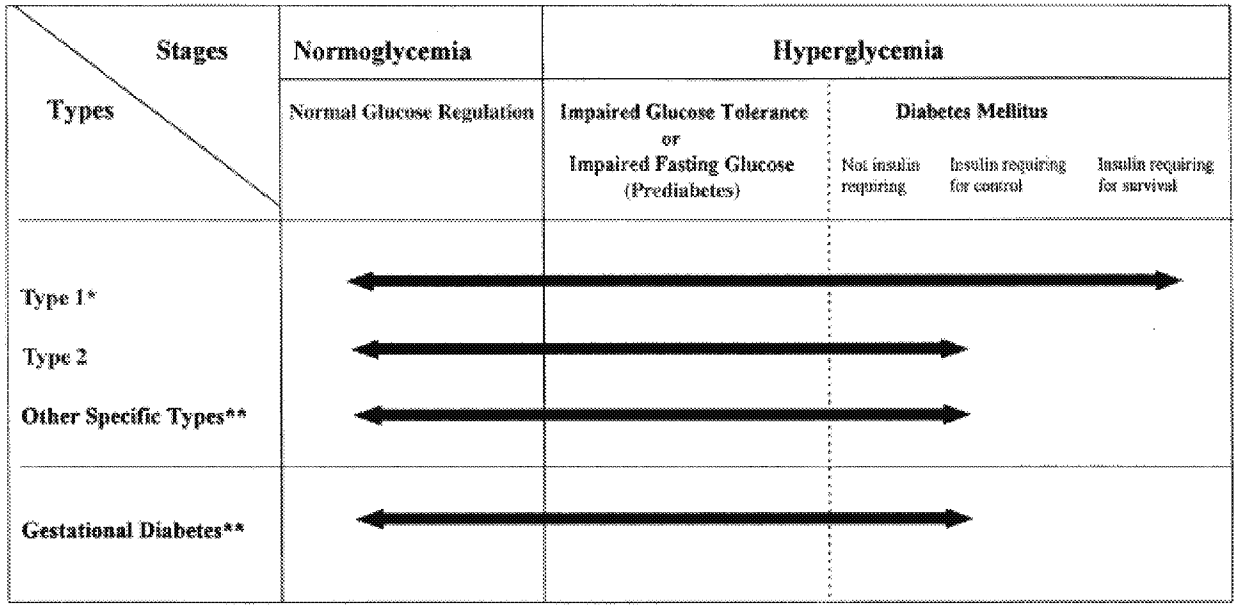
Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Metabolic Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and metabolic effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section 11P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2018).

Size Fraction	Causality Determination
Short-term exposure	
$PM_{2.5}$	Suggestive of, but not sufficient, to infer
$PM_{10-2.5}$	Suggestive of, but not sufficient, to infer
UFP	Inadequate
Long-term Exposure	
$PM_{2.5}$	Suggestive of, but not sufficient, to infer
$PM_{10-2.5}$	Suggestive of, but not sufficient, to infer
UFP	Inadequate

The evidence relevant to metabolic effects that was reviewed in the 2009 PM ISA included a small number of studies that examined the extent to which diabetes and metabolic syndrome-like phenotypes conferred susceptibility to PM-related health effects (U.S. EPA, 2009). Specifically, exaggerated insulin resistance, visceral adiposity and systemic inflammation in response to chronic exposure to CAPs was demonstrated in animals fed a high-fat diet. Epidemiologic studies reported some evidence for increased cardiovascular effects among people with diabetes or metabolic syndrome in association with PM_{10} exposure, providing preliminary evidence for pathophysiologic alterations experimentally demonstrated. There was no causal determination for metabolic effects in the 2009 ISA. The literature has expanded substantially with the bulk of evidence informing the relationship between long-term exposure to $PM_{2.5}$ and metabolic effects including glucose and insulin homeostasis and Type 2 diabetes (T2D).

The metabolic effects reviewed in this chapter include metabolic syndrome and its components (Table 7-1), diabetes (Table 7-2 and Figure 7-1), metabolic disease mortality as well as indicators of metabolic function that underlie metabolic and cardiovascular diseases. Studies that inform our understanding of whether people diagnosed with metabolic syndrome or diabetes are at increased risk of PM-related health effects are also discussed in CHAPTER 12, Section 12.3.2 (Populations and Lifestages Potentially at Increased Risk for PM Health Effects).



Note: *Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., "honeymoon" remission).

**In rare instances, patients in these categories (e.g., Vacor toxicity, Type 1 diabetes presenting in pregnancy) may require insulin for survival.

Source: Permission pending, ADA (2014).

Figure 7-1 Disorders of glycaemia: etiologic types and stages.

Metabolic syndrome is a term used to describe a collection of risk factors that include high blood pressure, dyslipidemia (elevated triglycerides and low levels of high density lipoprotein [HDL] cholesterol), obesity (particularly central obesity), and increased fasting blood glucose (FBG) (Table 7-1) (Alberti et al., 2009). The presence of these risk factors may predispose one to an increased risk of T2D and cardiovascular disease (see CHAPTER 6).

Table 7-1 Criteria for clinical diagnosis of Metabolic Syndrome

Risk Factor	Threshold
Waist circumference	≥89 cm in women and ≥102 cm in males
Triglycerides[a]	≥150 mg/dL (1.7 mmol/L)
HDL-C1	<40 mg/dL (1.0 mmol/L in males); <50 mg/dL (1.3 mmol) in females
Blood pressure[b]	Systolic ≥130 and/or diastolic ≥85 mm Hg
Fasting glucose[c]	≥100 mg/dL (5.6 mmol/L)

[a]A person taking drugs used to lower triglycerides or raise HDL-C is considered to exceed the threshold.
[b]A person taking blood pressure medication is considered to exceed the threshold.
[c]A person taking glucose regulating medication is considered to exceed the threshold.
Source: Permission pending, Adapted from Alberti et al. (2009).

Diabetes is characterized by a continuum of hyperglycemia (i.e., elevated glucose level) resulting from defects in insulin signaling, secretion or both (Figure 7-1). Several types of diabetes have been classified by the American Diabetes Association (ADA) (ADA, 2014). Type 1 diabetes (T1D) is caused by β-cell dysfunction or destruction that leads to insulin deficiency (Section 7.2.7), while T2D is characterized by defects in insulin secretion in an insulin resistant environment (Section 7.2.4). Gestational diabetes mellitus (GDM) is generally diagnosed during the 2nd or 3rd trimester of pregnancy (Section 7.2.6). The diagnostic testing criteria for diabetes are listed in Table 7-2. The A1C, which is also known as the hemoglobin A1C, HbA1C, or glycohemoglobin, is a blood test that provides information about a person's average blood glucose over the past 3 months by measuring the percentage of hemoglobin (i.e., a blood protein with a 3-month lifespan) modified by glucose. In controlled human exposure, animal toxicological, and epidemiologic studies the homeostasis model assessment (HOMA) model has been widely used for the quantification of insulin resistance (HOMA-IR) and pancreatic beta cell (HOMA-β) function and used to infer diabetes risk. The HOMA-IR index is given by the product of basal insulin and glucose levels divided by 22.5, whereas the HOMA-β index is derived from the product of 20 and basal insulin levels divided by glucose concentration minus 3.5 (Wallace et al., 2004; Matthews et al., 1985).

Table 7-2 Criteria for clinical diagnosis of diabetes.

Test	Criteria
A1C	A1C ≥6.5%[a]
	OR
Fasting Plasma Glucose (FPG)	FPG ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 h.[a]
	OR
Oral Glucose Tolerance Test (OGTT)	Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L during OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
	OR
Random Glucose Test	In a person with classical symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

[a]In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Diabetes test criteria were extracted from American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1): S81–S90

Impaired insulin signaling is a pathophysiological effect leading to clinical outcomes including insulin resistance, increased blood glucose, and increased blood lipids. Specifically, insulin stimulates sensitive tissues to take up glucose, lipids, and amino acids. In muscle, insulin stimulates glucose oxidation or storage as glycogen and protein synthesis; in liver, insulin stimulates glycogen synthesis; and in adipose tissue, insulin stimulates lipid synthesis and storage. During a fast (overnight) plasma glucose (60–80 mg/dL) and insulin (3–8 μU/mL) levels are low; glucagon levels rise and lipids are mobilized from adipose tissue into the circulation; glycogenolysis and gluconeogenesis increase in the liver; and striated muscle metabolizes lipids and degrades proteins into amino acids (Boron and Boulpaep, 2017). When individuals do not respond properly to glucose and insulin levels (as in T2D mellitus), body fuels (glucose, lipid, and amino acid) are mobilized into the blood, putting a burden on liver, kidney, and vascular function. For example, lipid oversupply promotes hepatic steatosis, hepatic fibrosis, and atherosclerosis, which is a major contributor to cardiovascular disease (see Section 6.3.4).

7.1 Short-Term $PM_{2.5}$ Exposure and Metabolic Effects

There were no epidemiologic or toxicological studies of short-term exposure to $PM_{2.5}$ and metabolic syndrome or diabetes included in the 2009 PM ISA. In the present ISA, there are a limited

number of epidemiologic studies examining the effects of short-term $PM_{2.5}$ exposure on glucose tolerance, insulin sensitivity, and diabetes control (i.e., HbA1c levels). A small number of experimental animal studies that evaluate $PM_{2.5}$-mediated effects on glucose and insulin homeostasis are also available for review. A limited body of controlled human exposure and toxicological studies also provide some evidence that diet and genetic factors, as well as systemic and peripheral inflammation, may play a role in the $PM_{2.5}$ mediated metabolic disruption. Collectively, these studies indicate that short-term exposure to $PM_{2.5}$ may affect glucose and insulin homeostasis.

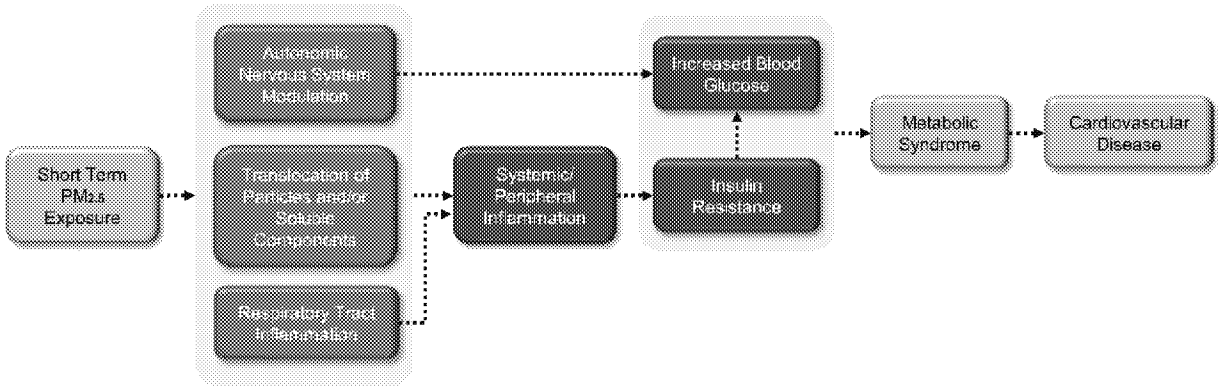
The discussion of short-term $PM_{2.5}$ exposure and metabolic effects opens with a discussion of biological plausibility (Section 7.1.1) that provides background for the subsequent sections in which groups of related endpoints are presented in the context of relevant disease pathways. These outcome groupings are glucose and insulin homeostasis (Section 7.1.2) and other indicators of metabolic function (Section 7.1.3). The collective body of evidence is integrated across and within scientific disciplines[68], and the rationale for the causality determination is outlined in Section 7.1.4.

7.1.1 Biological Plausibility

This section describes biological pathways that potentially underlie metabolic effects resulting from short-term exposure to $PM_{2.5}$. Figure 7-2 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{2.5}$ may lead to metabolic health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 7.1.

Progression from $PM_{2.5}$ exposure along the potential pathways depicted in Figure 7-2 are supported by experimental and observational evidence streams discussed below, as well as in other Chapters of the PM ISA including: dosimetry, respiratory, cardiovascular, and nervous system chapters (CHAPTER 4, CHAPTER 5, CHAPTER 6, and CHAPTER 8, respectively). CHAPTER 4 discusses the PM administered dose dependence on deposition, which is a function of particle size, intake, and physical chemistry as well as modifying factors such as lifestages and species. The available evidence for $PM_{2.5}$ is organized into potential pathways that include autonomic nervous system (ANS) modulation, translocation of soluble components and respiratory tract inflammation that converge upon systemic inflammation leading to insulin resistance and metabolic risk factors, metabolic syndrome, or comorbidities. Although the specific details underlying these proposed pathways are unclear, evidence from experimental and epidemiologic studies implicate relationships between short term $PM_{2.5}$ exposure and metabolic effects. Further, metabolic syndrome risk factors can lead to complications and comorbidities.

[68] As detailed in the Preface, risk estimates are for a 10 $\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations unless otherwise noted.



The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 7-2 Potential biological pathways for metabolic effects following short-term $PM_{2.5}$ exposure.

The central nervous system (CNS) and ANS pathways have the potential for activation due to stimulation of sensory nerves that are further described in CHAPTER 4 and CHAPTER 8. Soluble components of $PM_{2.5}$, and poorly soluble particles that are part of the $PM_{2.5}$ fraction and smaller than approximately 200 nm, may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments (CHAPTER 4). The extent to which translocation into the systemic circulation occurs is currently uncertain. A study from the 2009 PM ISA (Campbell et al., 2005) described a proinflammatory response in the brain that was accompanied by increases in cytokines TNFα and IL-1α that functionally stimulate and enhance the inflammatory response (see CHAPTER 8). More recent evidence describes promotion of inflammatory gene expression (Section 8.1.3.2), and it is possible that these immune signaling molecules may initiate an innate immune response transmitted through the circulation to other organs tissues. Furthermore, Balasubramanian et al. (2013) found that $PM_{2.5}$ increased the neurotransmitter norepinephrine and the endocrine hormone corticotrophin releasing hormone (CRH) in the hypothalamus. Although Balasubramanian et al. (2013) measured norepinephrine hours after exposure, an increase in the neurotransmitter may mobilize the ANS. The ANS may activate a "flight or fight" response that not only increases vasoconstriction, heart rate and blood pressure, but also mobilizes glucose into the blood stream. Similarly, CRH release stimulates glucocorticoid synthesis marked by a stress response that leads to mobilization of energy stores (i.e., glucose and lipids) into the blood stream (Section 7.1.2.2).

Respiratory tract inflammation leading to inflammatory mediator diffusion from the lung is another potential part of a pathway leading to systemic inflammation (see CHAPTER 5 and CHAPTER

6), systemic oxidative stress, and peripheral inflammation, as indicated by Kim et al. (2015) from human liver function measures (Section 7.1.4) and Sun et al. (2013) from rodent adipose tissue. Once in the circulation inflammatory mediators (such as cytokines, damage associated molecular patterns [DAMPs], and oxidized lipids) may further stimulate the immune response by interacting with endothelium leading to coordination of immune signaling from the circulatory system into peripheral tissues. Short term $PM_{2.5}$ exposure reduced the antioxidant and anti-inflammatory capacity of HDL particles (CHAPTER 6) (Hazucha et al., 2013). These collective responses can stimulate the migratory capacity and increase infiltration of inflammatory cells as demonstrated by Xu et al. (2013) (Section 7.1.3.1), but also interfere with insulin signaling by stimulating the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκβ) pathway via toll-like receptor (TLR) activation (further discussed in Section 7.2.1). Of note, TLR activation interfered with insulin-mediated stimulation of the IRS/PI3K/Akt signaling pathway leading to impaired expression and/or function of insulin signaling components (de Luca and Olefsky, 2008). Further, Haberzettl et al. (2016) identified that short-term $PM_{2.5}$ exposure led to insulin resistance in aortas as measured by failure of insulin to stimulate Akt phosphorylation in mice. Collectively, these findings provide a potential pathway connecting systemic and peripheral inflammation to insulin resistance. Consistent with these experimental animal findings Brook et al. (2013b) reported an association of short-term exposure to $PM_{2.5}$ with increased glucose, insulin and HOMA-IR among healthy subjects and Zanobetti et al. (2014) reported a small increase in hospital admissions for diabetes in association with short-term exposure to $PM_{2.5}$.

As described here, there are proposed pathways by which short-term exposure to $PM_{2.5}$ could lead to metabolic health effects. One pathway involves CNS and ANS activation, translocation of soluble components, and pulmonary inflammation that may lead to systemic inflammation and inflammation of other peripheral organs that is linked to insulin resistance and metabolic syndrome comorbidities. ANS modulation that can also lead to activation of a "flight-or-fight" response increasing blood glucose that is linked to metabolic syndrome. While experimental studies involving animals contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term $PM_{2.5}$ exposure and both insulin resistance and cardiovascular disease endpoints. Together, these proposed pathways provide biological plausibility for epidemiologic results of metabolic health effects and will be used to support a causal determination, which is discussed later in the chapter (Section 7.1.4).

7.1.2 Glucose and Insulin Homeostasis

Insulin is secreted by β-cells within the pancreas in response to glucose levels. When glucose levels rise, depolarization of the pancreatic β-cells or modulation by other hormones stimulate insulin secretion. Thus, during feeding, blood insulin levels rise stimulating glucose uptake and replenishment of body fuel reserves in the form of triglycerides and glycogen. When insulin levels decrease (e.g., during fasting) fuels such as lipids from adipose tissue and amino acids from muscle are mobilized to the blood

stream where they are used by the liver to synthesize glucose (Section 7.1.1). Notably, the effects of short-term exposure to $PM_{2.5}$ on glucose and insulin homeostasis may be transient.

7.1.2.1 Epidemiologic Studies

Several epidemiologic studies examined the relationship of short-term exposure to $PM_{2.5}$ with indicators of glucose and insulin homeostasis (Table 7-3). Peng et al. (2016) found that short-term exposures (i.e., 1-, 7- and 28-day averages) were associated with increased FBG and a higher odds of impaired fasting glucose (IFG), defined as fasting blood glucose <100 mg/dL. These authors also reported that ICAM-1 promotor methylation mediated the association with 28-day average exposure to $PM_{2.5}$ and FBG. Brook et al. (2013b) reported increased glucose, insulin and HOMA-IR among healthy subjects exposed to $PM_{2.5}$ during 5-day exposure blocks. Lucht et al. (2018b) reported an increase in blood glucose level [0.80 mg/dL (95% CI: 0.33, 1.26)] in association with 28-day average $PM_{2.5}$ exposure among those without diabetes enrolled in the Heinz Nixdorf Recall (HNR) study. An association of HbA1c with 91-day average $PM_{2.5}$ exposure was also observed in this study (see Section 7.2.3). Results from a large retrospective cohort study in Israel did not report evidence to support associations of 24-hour or 7-day average $PM_{2.5}$ exposure with glucose level, glycated hemoglobin (HbA1c), or lipids, although a 3-month average exposure was associated with HbA1c and lipid level (Yitshak Sade et al., 2016) (see Section 7.2.3). Finally, Zanobetti et al. (2014) reported an increase in hospitalizations for diabetes in association with 2-day average concentrations of $PM_{2.5}$ (RR: 1.01 [95% CI: 1.00, 1.02]) most likely reflecting the risk of diabetes-related complications among those with diabetes. Overall, the small number of studies indicate that short-term exposure to $PM_{2.5}$ (1−7 days) may affect glucose and insulin levels among those without diabetes, and consequent increases in hospital admissions for conditions related to diabetes. None of these studies examined the extent to which confounding by copollutants may have influenced their findings.

Table 7-3 Epidemiologic studies of short-term exposure to $PM_{2.5}$ and effects on glucose and insulin homeostasis.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Peng et al. (2016) $PM_{2.5}$: 2000–2011	NAS N = 551 older men without diabetes	1-, 7-, 28-day avg preceding clinic visit, satellite derived AOD with LUR C-V R^2 = 0.81	1-day mean 10.92 (SD 5.42) 7-day mean 10.59 (3.48) 28-day mean 10.71 (2.62)	FBG IBG (FBG > 100 mg/dl)	Correlations (*r*): NR Copollutant models: NR
†Brook et al. (2013b) Dearborn, Michigan $PM_{2.5}$: June-Aug 2009/10	N = 25 healthy adults (18–50 yr) residing in rural location	5-day urban exposure	11.5 (SD: 4.8)	HOMA-IR Glucose, insulin, HRV, arterial stiffness	Correlations (*r*): NR Copollutant models: NR
†Lucht et al. (2018b) Ruhr area, Germany $PM_{2.5}$: 2000–2008	HNR study N = 4,176 Nondiabetic	EURAD model, 1 km grid cell *r* = 0.51–0.61, modeled and measured concentrations (Wurzler et al., 2004)	28-day mean = 17.4 IQR = 5.7	Blood glucose level	Correlations (*r*): *r* = 0.73 NO_2; *r* = 0.89 PM_{10} Copollutant models: NR
†Yitshak Sade et al. (2016) $PM_{2.5}$: 2003–2012	N = 73,117 Residents of southern Israel	24 h, 7 days, 3 mo concentration, satellite derived AOD, 1 × 1 km grid of residential address C-V R^2 = 0.72	24 h and 7-day concentrations NR	Glucose HbA1c Lipids	Correlations (*r*): NR Copollutant models: NR
†Zanobetti et al. (2014) 121 Communities, U.S. 1999–2010	Medicare >65 yr old	2-day avg for community, one or more monitors	NR (community specific only)	HAED visits for Diabetes (ICD9: 250)	Correlations (*r*): NR Copollutant models: NR

AOD = Aerosol Optical Density, avg = average, C-V = cross validated, EURAD = European Air Pollution Dispersion, FBG = Fasting Blood Glucose, HOMA-IR = Homeostatic Model Assessment Insulin Resistance, HbA1c = glycated hemoglobin, IBG = Impaired Blood Glucose, ICD = International Classification of Disease, IGT = impaired glucose tolerance, LUR = Land Use Regression, NR = Not Reported.

†Studies published since the 2009 PM ISA.

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